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An Investigation of Anodic Coupling Reactions

submitted by J.A.Wyatt

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Summary

The theory and application of anodic oxidation is summarized and the literature relevant to this study is briefly reviewed.

The synthesis of several dibenz[c,e]azocin-7-ones and dibenz[c,e]azepin-5-ones is described (Chapter 1). Practical difficulties were encountered during the oxidation of some secondary amides and esters, and with the evidence supplied from cyclic voltammetry, benzylic oxidation is proposed as a major problem.

Attempts to synthesise the alkaloid, lycorine, by the oxidative coupling of several 1-substituted oxindoles were unsuccessful but the anodic oxidation of 3-substituted oxindoles and indoles afforded several compounds of novel structure. The first reported electrochemical oxidation of an indoline to an indole is described.

Anodic oxidation of diarylesters yielded only intermolecularly coupled products, some of which proved to be ortho and para quinones. A mechanism for their formation based upon cyclic voltammetric evidence is proposed.

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Introduction

Oxidative electro-organic chemistry is certainly not new; it has its origins in the middle of the last century when Kolbe[1] studied the synthesis of alkanes by the electrolysis of the alkali metal salts of carboxylic acids. The basic equation for this reaction is as follows:

$$2RCO_2^- \xrightarrow{-\ 2e^-} 2RCO_2^{\bullet} \longrightarrow 2R^{\bullet} + 2CO_2$$

$$2R^{\bullet} \longrightarrow R\text{-}R$$

The Kolbe synthesis has received much attention from organic chemists[2], mainly due to the wide variety of acids that undergo coupling, together with the simple experimental conditions needed. In the early nineteen hundreds, small scale industrial electrochemical processes were in use for the preparation of intermediates, such as benzidine and anthraquinone[3,4], but from then until the middle of the century there followed an apparent lack of interest in anodic oxidation. Several reasons may be advanced to explain this neglect but the main one almost certainly was the non-availability of instrumentation, particularly of the type which would allow the quantitative assessment of oxidation potentials, the number of electrons being removed at a particular potential and the probable sequence of events occurring after oxidation. In short, a means to interpret the mechanism of complex anodic processes. Similar problems also beset the development of reductive techniques, but at least in this case, polarography[5,6] was well established as an analytical method and some progress was achieved in the interpretation of electrochemical processes at the cathode.

Necessity is of course the mother of invention, and a further restraint was the reluctance of organic chemists to consider electrochemical reactions as alternatives for more conventional chemical reagents, despite the fact that addition or removal of electrons is fundamental to all chemical reactions.

To a large extent, irreversible electron transfer reactions occur in organic electrochemistry because of fast secondary chemical processes, and for this reason attempts to apply classical theoretical concepts based on reversibility (e.g., the Nernst equation) failed. This led to the examination and mathematical description of irreversible electrode processes, first quantified by Tafel[7] (see page 20).

A broad spectrum study of organic electrochemistry would obviously be a mammoth task, involving an assessment of both reduction and oxidation. Therefore, a considerable degree of specialization in one aspect of the subject is not only desirable, but essential if any advance in the understanding of electro-organic synthesis is to be achieved. This thesis therefore, is concerned with the anodic oxidation of organic substrates, and more specifically, the aim has been to design substrates suitable for oxidative coupling.

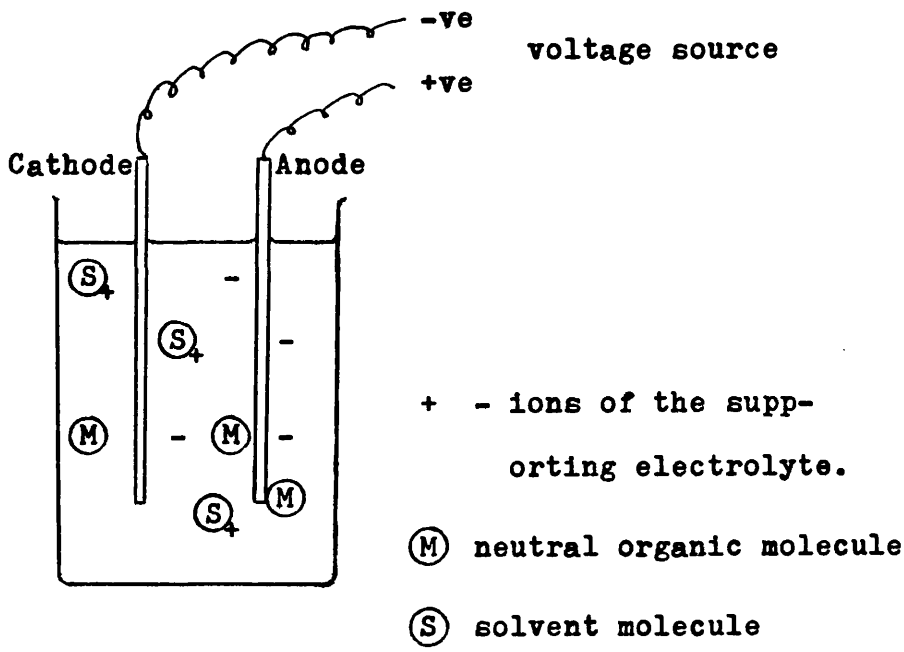
Clearly the term oxidative coupling is still sufficiently abstract to include such work as the Kolbe type synthesis and the coupling of aliphatic and alicyclic structures, but in all the work described the chief purpose has been to couple two aryl nuclei together in either an inter- or intra-molecular manner.

Before embarking upon a more detailed account of the type of reactions studied, it is necessary to introduce some of the basic laws of electrolysis, together with a description of the various analytical and experimental procedures employed. It would be foolish for the organic chemist interested in electrochemical methods of synthesis to ignore the importance of such factors as electrode potential and the effect that the double layer can have on product distribution and so this brief introduction is considered as essential, to the understanding of many of the points made later in the discussion. The overall emphasis of this thesis, however, is to use the technique of anodic oxidation to synthesise substrates upon which further chemistry can be conducted.

(1) The Electrochemical Cell - For all electrochemical reactions a suitably designed cell is mandatory, but for many, a simple one compartment cell (figure 1) is quite adequate[8]. This basic arrangement has both electrodes, the anode and the cathode immersed in a conducting solution namely the electrolyte which is usually a combination of a solvent and a solute (supporting electrolyte), but occasionally the solvent is sufficiently conducting that a supporting electrolyte is not needed.

On applying a potential difference between electrodes a current flows and electrolysis occurs. This current flow through the system involves firstly, electronic

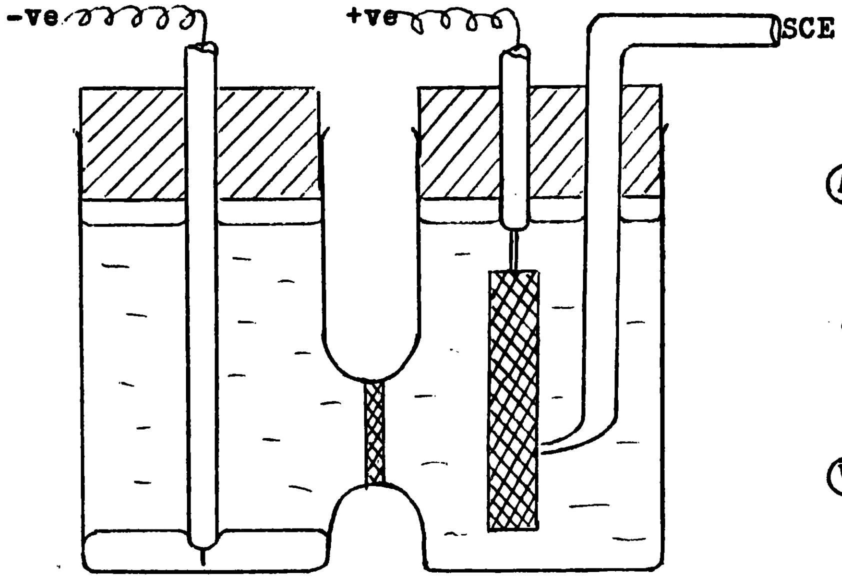
Figure 1



conduction through the external elements of the circuit followed by ionic conduction, which involves the movement of dissociated ions in solution under the influence of an electrostatic field. Finally, electron transfer occurs either to or from the electrode to the species (M) at the cathode and anode respectively.

Clearly, in a "one" compartment cell as shown in Fig. 1, there is the possibility of both cathodic reduction and anodic oxidation of the substrate. To overcome this problem a two compartment cell (Fig. 2) may be used in which the sections are divided by a glass frit (other materials have been used)[9]. This frit is porous enough for ionic conduction but not sufficiently permeable for diffusion of the substrate.

Figure 2



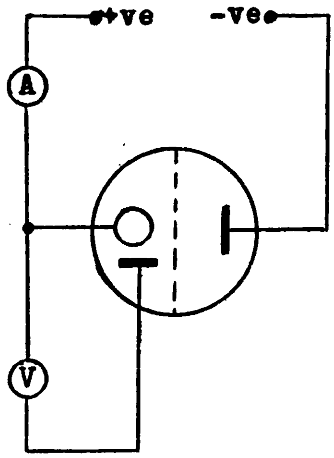


Figure 2a.

Figure 2 shows a typical two compartment, three electrode H-type cell used for a controlled potential electrolysis. The left-hand compartment contains the cathode (referred to as the counter electrode in anodic oxidations) and thus the solution in this half of the cell is referred to as the catholyte. In anodic oxidations the nature of the counter electrode is not critical, providing it is chemically inert under the experimental conditions, a mercury pool, a stainless steel plate[10] or a platinum gauze[11] are commonly employed. The other half of the cell contains the anode immersed in the anolyte together with a reference electrode, (the latter does not partake in any Faradiac process occurring in the cell). Restrictions on anode materials are far greater than for their cathodic counterparts; this limitation is caused by the fact that most metals are themselves oxidized at fairly low electrode potentials. Platinum (and the platinum group metals), however, exhibit good characteristics in this respect and hence may be used as anodes in electro-organic reactions at fairly high electrode potentials, other electrodes such as carbon[12] and lead dioxide[13] have also commonly been used.

The purpose of the reference electrode is to monitor the electrode potential of the anode during a preparative electrolysis. The electrode potential is simply the difference in voltage between the anode surface and the solution directly adjacent to it, therefore the closer the reference electrode is to the anode surface, the more accurate will be the measure of electrode potential.

Some theoretical considerations

As only minute quantities of current pass through the reference electrode circuit (Fig. 2a) it is important to use a high impedence voltmeter, otherwise inconsistent and erroneous readings will be indicated.

The electrode potential has a profound effect on the kinetics of the electrochemical reaction, or more properly the rate of electron transfer to, or from the substrate. To make a "chemical" analogy, electrons can be regarded as the reagent and the electrode potential thus controls the availability of the reagent.

It is well known that when a metal is placed in a solution an equilibrium is established between its ionized and unionized forms.

$$M \rightleftharpoons M^{n+} + ne^- \qquad (1)$$

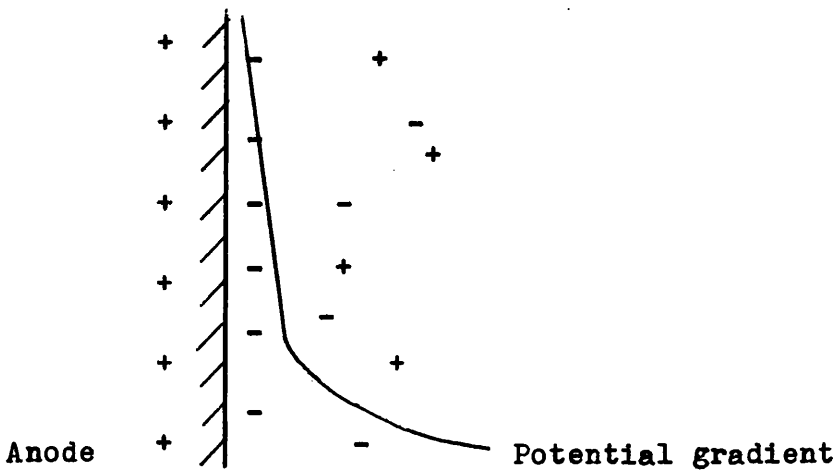
For example, with the alkali metals in aqueous solution, the equilibrium in equation (1) lies far to the right-hand side, however, with the noble metals the equilibrium concentration of ions is extremely low. If, however, an excess polarizing charge is placed on the noble metal (as in an electrochemical cell) the equilibrium is momentarily disturbed, but the ions in the solution quickly respond and form a layer of counter ions, thus re-establishing equilibrium conditions. This layer of counter ions is referred to as the double layer. The charging of the electrode surface in this way is not dissimilar to the charging of a parallel plate capacitor and hence the charging current (C_{dl}) is given by equation (2).

$$C_{dl} = \frac{\varepsilon}{4\pi d} \qquad (2)$$

C_{dl} = Capacity per unit area
ε = Dielectric constant of the medium
d = Thickness of the double layer

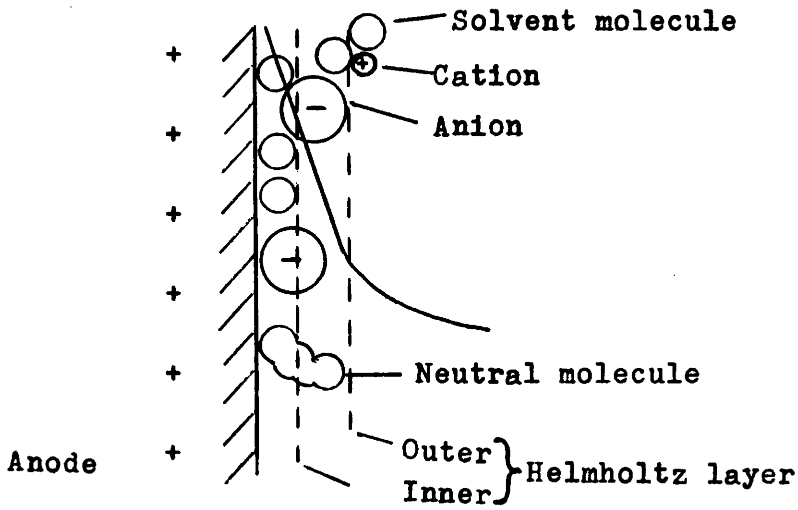
The formation of the double layer is a purely electrostatic effect and therefore does not involve the net transfer of current[14]. Helmholtz proposed the simplest description of the double layer suggesting that a rigid fixed layer of counter ions exists near the electrode, but away from this there is a sharp fall in electric potential. A more realistic approach was forwarded by Stern[15], who proposed that both a rigid fixed, and diffused mobile layer of counter ions surrounds the charged electrode (Fig. 3).

Figure 3

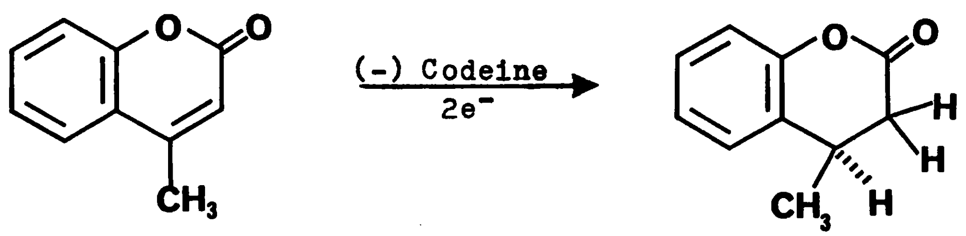


Even this is not completely satisfactory and a more updated approach has been forwarded by Grahame[16], who has taken into account the differences between anions and cations in solution, the latter are tightly bound by a shell of solvent molecules. On the other hand, anions, are generally larger, and because of their more polarizable nature can approach more closely the electrode surface. Figure 4 is thus probably most representative of the real situation[17].

Figure 4



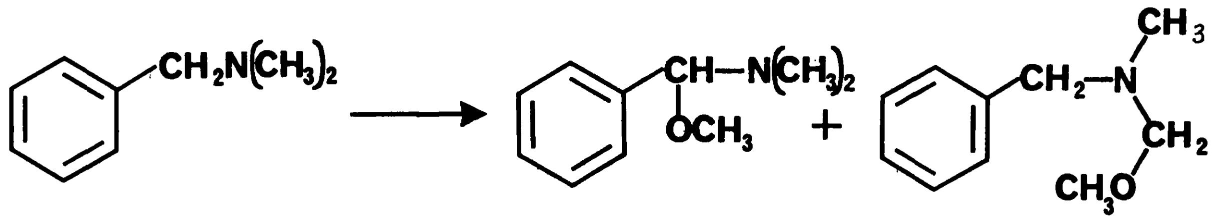
The alkali metal cations have a particularly strong solvation shell, and thus it would be expected that different electrolytes would alter the nature of the electrical double layer. This is indeed so, and in some cases it can alter both the nature of the product[18] obtained from the electrolysis and its stereochemistry. Thus the major product in the electroreduction of acrylonitrile in aqueous solution is adiponitrile only when the supporting electrolyte is a quaternary ammonium salt[18]. The presence of an optically active organic molecule which is itself electrochemically inert can promote the formation of optically active products, thus the electroreduction of 4-methylcoumarin in the presence of (-) codeine affords optically active 3, 4-dihydro-4-methylcoumarin[19].



The effect and strength of adsorption can also alter product distribution[20] and the kinetics of the reaction[21]. Adsorption is said to occur whenever the concentration of substrate at the electrode surface is greater than the concentration in the bulk phase, and the attraction forces may be either van der Waals forces (physical adsorption) or the formation of actual chemical bonds (chemisorption), the latter mainly occurring with the platinum group metals[22].

The chemisorption of reactants and intermediates may be a possible cause of electrode filming problems so often encountered when using noble metals as electrodes[23].

For an electron transfer to occur between the substrate and the anode the neutral species must of necessity come within close proximity of the electrode surface. At small distances from the electrode surface (~ 5Å) the electrostatic field is extremely large and this may cause a temporary distortion of the electronic nature of the molecule,in short, a momentary dipole is induced, and the formation of this dipole will then cause the molecule to take up a preferential orientation towards the electrode surface. Furthermore, any permanent dipole that already exists in the molecule will be reinforced by the momentarily induced dipole and Weinberg has suggested that this is the reason for the abnormal distribution of the two products (3) and (4) from the anodic methoxylation of N,N-dimethylbenzylamine[20]. Weinberg proposes that the

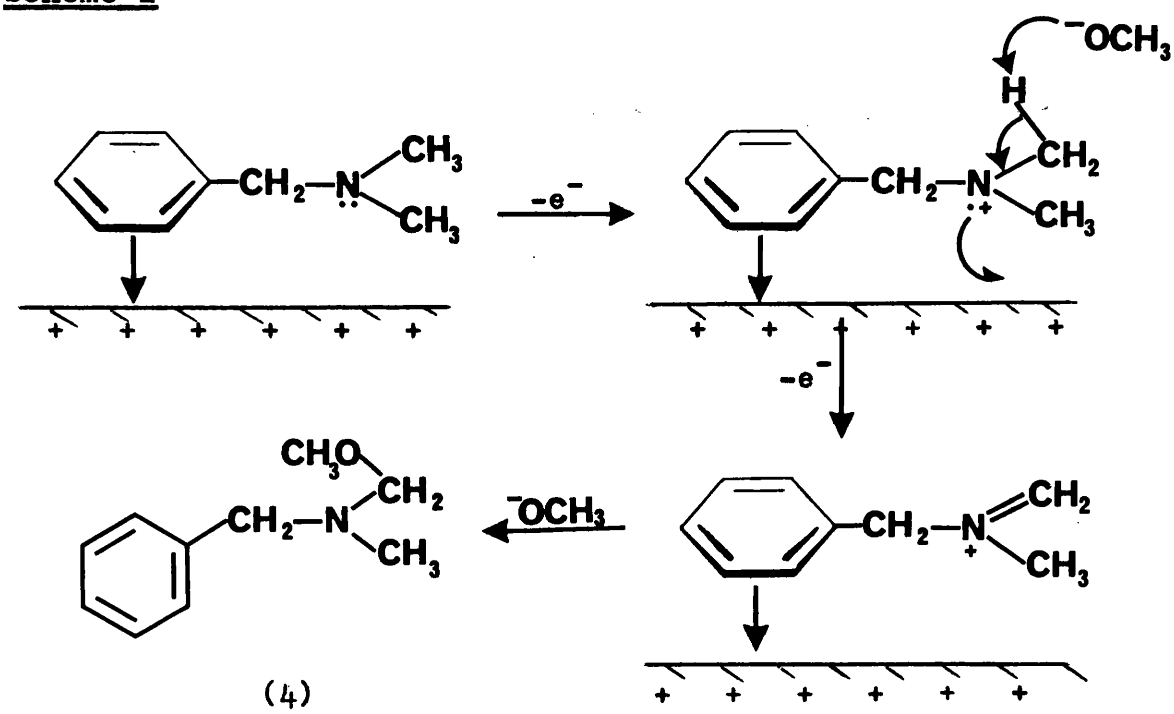


(3) (4)

Major Product

benzylic $-CH_2-$ unit is not involved because its hydrogen atoms are close to the electrode surface; thus the methoxide ion preferentially attacks one of the methyl groups to give the less favourable iminium ion (5) (Scheme 1)[20].

Scheme 1



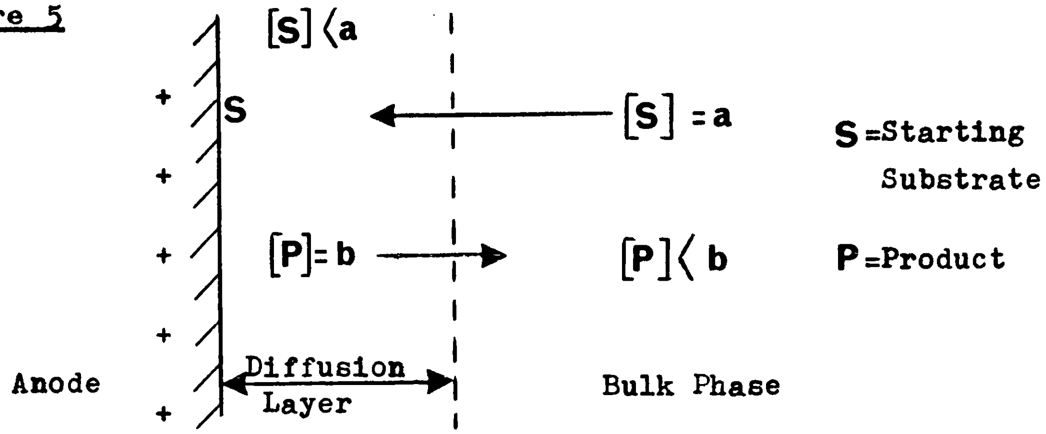
(4)

(5)

A consideration of modes of transport to, and from the electrode surface within an electrolyte is clearly of practical importance to the electrochemist. Three forms of transport are recognised and can be classified under the headings: migration, diffusion and convection. Migration is simply the passage of charged particles moving within the influence of an electrical field. During an electrolysis, it is the migration of the ions of the supporting electrolyte which carries the current through the cell. Migration is only normally significant for small inorganic ions, since larger organic ions move slowly in applied electrostatic fields.

Diffusion occurs where there are localized concentration gradients; normally the larger the gradient the greater the rate of diffusion. Consider a substrate (S) which is oxidized at the electrode surface and forms a chemical product (P). In the region near the electrode where diffision currents are established (0.003-0.1cm) the concentration of substrate (S) will be less than in the bulk phase and hence substrate will diffuse towards the

<u>Figure 5</u>



electrode surface (Fig. 5). On the other hand the product (P) will diffuse away from the electrode into the bulk phase where its concentration is less.

Transport of the substrate by convection is caused by thermal gradients, stirring, or mechanical agitation, therefore it is the process over which the experimenter has most control, and through the judicious choice of the right combination of these variables the product yield may be improved considerably.

Figure 6 in a generalized way indicates the overall picture of the regions around the anode during an electrolysis reaction[24] and provides a summary of some of the points raised in the above account.

Figure 6

Electron transfer occurs here.	Significant charge separation in this region (Potential Gradient). Preferential population by counter ions. Here the abundance of anions leads to loss of electro neutrality.	Concentration gradients for product and reactant are established as the reaction proceeds.	Migration of charged particles. (Movement of neutral species by convection).
0.5-2.0A^{o}	3.5-1000A^{o}	0.003-0.1cm	
REACTION LAYER	ELECTRICAL DOUBLE LAYER	DIFFUSION LAYER	BULK SOLUTION

Practical Requirements

Before embarking further upon other fundamental electrochemical relationships, it is worthwhile mentioning some of the practical aspects and restrictions appertaining to this work.

Due to the insolubility of most organic compounds in aqueous media, organic solvents must form the basis of the electrolyte system. Even if the organic substrate were soluble in water, its use as an electrolyte is highly undesirable due to the high reactivity of water itself towards both cations and cation radicals, which necessarily are intermediates in anodic reactions. Therefore, the ideal electrolyte solvent must fulfill several requirements.

1. It must be electrochemically inert in the potential range of the experiment.
2. It must be a good solvent for organic substrates.
3. It must be unreactive towards the intermediates present in an electrochemical process.
4. It must have a fairly high dielectric constant.
5. It must be comparatively easily purified and dried.

Most of these criteria are self-explanatory, but the need for a solvent with a high dielectric constant is necessary to minimize the electrolytes electrical resistance. Needless to say, there are few solvents that fulfill all of these demands, but acetonitrile is almost certainly one of the most commonly employed, and is not oxidised below +2.0v when a perchlorate salt supporting electrolyte[25] is used. Other commonly used solvents include dichloromethane[26] and trifluoroacetic acid which are reported to have some advantages over acetonitrile, particularly as trifluoroacetic acid is known to stabilize radical cation intermediates[27].

The restrictions placed on the supporting electrolyte are similar to those for the solvent, but additionally, solubility in the solvent is, of course, an important factor. The most common electrolytes are alkali metal perchlorates[28] and tetra-n-alkyl ammonium fluoroborates[28]. The choice of a particular solvent often restricts the type of supporting electrolyte that may be used, thus for example, tetra-n-butyl ammonium salts are used in combination with low polarity solvents such as dichloromethane.

Considerations of the electrode "layout" within the cell must also be taken into consideration as yields of products may be affected by poor positioning. For the minimum electrical resistance in the cell the distance between the anode and cathode should be as small as possible. Furthermore, all parts of the anode should be equidistant from the cathode since regional differences in current density may give rise to varying electrode potentials across the anode surface. In practice, using an H -type cell with a mercury pool counter electrode and a platinum gauze anode, it is difficult to obtain complete uniformity[29], and therefore the reference electrode should be placed in such a position that the highest potential is observed.

The external voltage applied to the cell, necessary to maintain a practical rate of electrolysis, clearly depends on the electrical resistivity of the electrolyte. Thus, when solvents such as dichloromethane are employed, which have low dielectric constants, larger concentrations of electrolytes are desirable otherwise excessive heat may be evolved. This is particularly important in the region of the glass frit where the electrical resistance is highest. The formation of surplus heat in electrochemical cells is more often a problem encountered in industrial processes and can easily be surmounted in the laboratory by the use of a water jacket and efficient stirring.

The degree of reproducibility of an electrooxidation will also depend on the condition of the electrode surface. Platinum was believed to be inert towards oxidation but cyclic voltammetry studies conducted by Brietens *et al*. has shown that the platinum metal solution interface (called the double layer domain) only exists between a narrow range of electrode potentials (0.40v-0.80v)[30]. Above 0.80v the metal surface is covered with oxides of platinum, while below 0.40v hydrogen is absorbed onto the metal surface. Therefore, the need to ensure that the electrode is chemically clean is most important, we have found this to be particularly true of platinum electrodes used for cyclic voltammetric studies[31].

The saturated calomel electrode[32] (SCE) is the most commonly used reference electrode; it consists of mercurous ions in contact with a saturated solution of potassium chloride and gives rise to a potential of 0.24v when measured against the hydrogen electrode. Mercurous chloride is unstable in the presence of acetonitrile and therefore calomel reference electrodes are usually connected *via* a conducting salt bridge (typically KCl/Agar) to the organic electrolyte. Many workers prefer the "more manageable" silver/silver chloride electrode[33], particularly when conducting cyclic voltammetry experiments where the silver electrode can be placed into close proximity of the working electrode.

Some Basic Electrochemical Laws.

From the beginning of the nineteenth century, when the first electrochemical experiments were conducted, attempts have been made to represent practical observations by theorical equations. As early as 1834, Faraday[34] described the relationship between the quantity of electricity consumed in an electrolysis and the amount of material used thus:

1. The amount of material transformed is proportional to the quantity of electricity passed.
2. The weights of the various materials transformed are proportional to their respective equivalent weights.

Naturally these two fundamental relationships are known as Faraday's laws and are represented collectively in equation 1.

$$W = M \frac{Q}{96{,}500n} \tag{1}$$

W = weight of material transformed

Q = quantity of electricity in coulombs

M = molecular weight of the substrate

n = number of electrons transferred per mol

The number 96,500 is referred to as one "Faraday", and is simply the number of coulombs necessary to transform one mol of substrate in a one electron reaction (i.e., 1F/mol). Rarely does the consumption of 1F/mol of current result in the formation of one mol of product; this arises from the fact that electrochemical reactions are not 100% efficient, and losses in heat and electrochemical side reactions of the solvent must be taken into account. This does not imply, however, that the chemical efficiency of an electrochemical reaction cannot reach close to 100%, indeed some reduction processes approach this value[35,36]. Thus the electrical efficiency (E.E.) can be represented by equation 2 (in terms of the symbols already described).

$$E.E. = \frac{96{,}500 \quad n}{M.Q.} \tag{2}$$

Nernst studied the relationship (for reversible electrode processes) between the electrode potential and the concentration of electroactive species in solution. His findings showed that at any value of current, the reversible electrode potential (E_R) was solely dependent upon the concentrations of oxidizable [Ox] and reducible [Red] species at the electrode surface. These considerations gave rise to the now familiar Nernst equation.

$$E_R = E^o{}_R - \frac{RT}{2F} \ln \frac{[Ox]}{[Red]}$$

Consider in the above equilibrium (i.e., Red $\rightleftharpoons$ Ox +ze$^-$), that the concentrations of oxidized and reduced species are equal i.e. [Red] = [Ox] . In this case, the Nernst equation predicts that the electrode potential (E_R) will equal the standard electrode potential ($E^o{}_R$). If, however, E_R is made more positive with respect to ($E^o{}_R$), the "second term" in the equation must also increase by an equal amount for equilibrium conditions to be maintained. This implies that the ratio $\frac{[Ox]}{[Red]}$ must increase (oxidation occurs) and hence a transfer of electrons occurs as the equilibrium moves from left to right. This equilibrium can be maintained because more reduced species will diffuse to the electrodes surface from the bulk phase. The difference between the electrode potential when the current is flowing, and that when there is no current is referred to as the concentration overvoltage for a reversible system.

Stable reversible systems in organic electrode processes are rather the exception than the 'norm' and hence the term overpotential (η) is described as being the extra potential required to drive the reaction in the forward direction (Equation 3). The greater the overpotential, the faster the electrode reaction occurs and the more irreversible it becomes:

$$\eta = E - E^o \qquad (3)$$

E = observed electrode potential

E^o = standard electrode potential

For many organic electrode reactions, E^o is unknown and hence measurements of the overpotential with respect to a reference electrode are substituted.

The overpotential is directly related to the cell current (i) (Equation 4),

$$i = i_o \exp\left(\frac{\alpha F E^1}{RT}\right) \qquad (4)$$

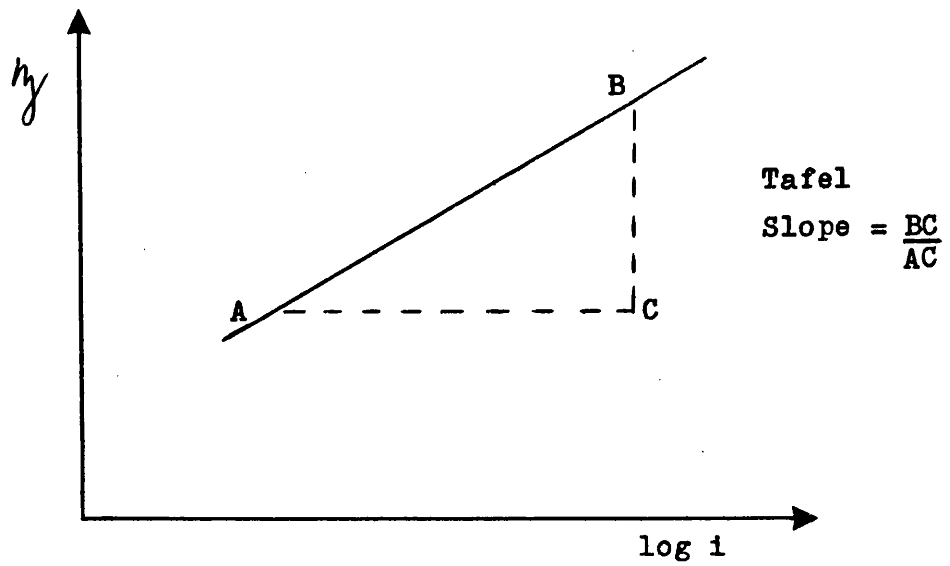
α = transfer coefficient

i_o = exchange current density

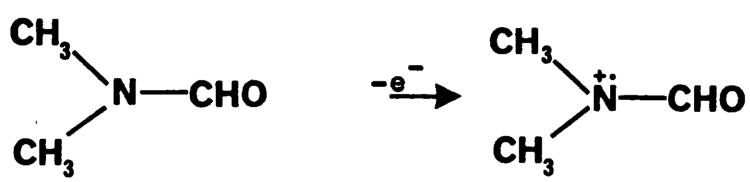
$\eta = E^1 = E - E_{REF}$

A plot of η against log i gives rise to the familiar Tafel graph, (Figure 7). The construction of Tafel lines can sometimes be used to show that the critical kinetic step in an electrochemical reaction is the initial electron transfer.

Figure 7



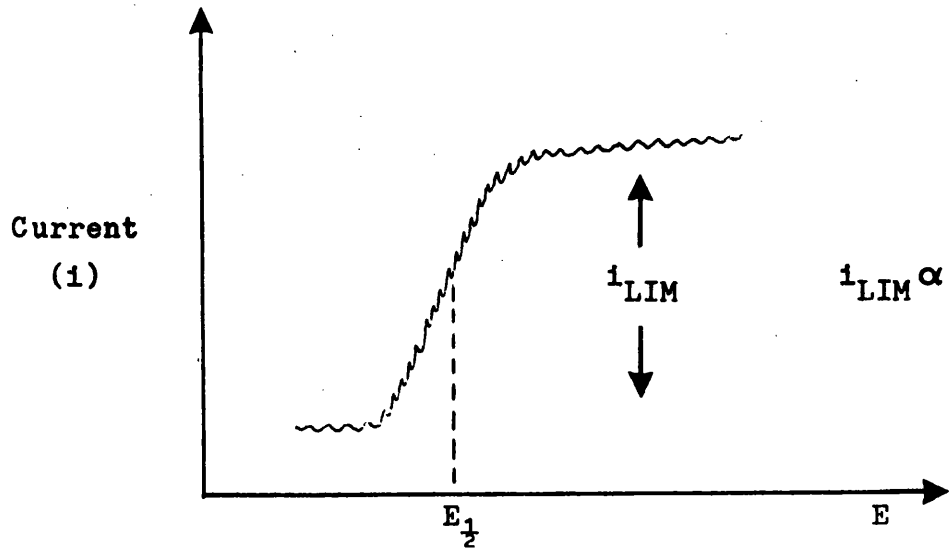
If this is so, a Tafel slope of 120mV will be obtained i.e., the current density undergoes a tenfold increase with a 120mV rise in overpotential. Ross et al. have used this argument to demonstrate that the rate determining step in the electrooxidation of dimethylformamide is also the first i.e., the formation of the cation radical [37].



Electroanalytical Techniques:

Various electroanalytical techniques are now available to investigate the mechanisms which occur at the electrode surface. Classical polarography, first introduced by Heyrovsky[5] in the 1920's, has been largely superseded by linear sweep voltammetry and triangular wave voltammetry. Further, the introduction of new types of microelectrodes is making the study of electrode kinetics considerably easier. In polarography the current through a dropping mercury electrode (D.M.E.) is monitored while a gradual linear change in electrode potential is made. A typical current/potential plot is illustrated in Figure 8 wherein the rate of the reaction is dependent on the electrode potential. As the voltage rises, current begins to flow at the appropriate oxidation potential and as the voltage continues to rise, the rate of the reaction exceeds the diffusion supply. At this point the concentration of substrate at the electrode surface approaches zero and no further increase in current is observed.

Figure 8



An expression which determines the maximum diffusion limiting current of a polarographic peak has been derived by Ilkovic[38], but this is of little relevance to the discussion. Of much more importance is a description of linear scan voltammetry and the closely related cyclic voltammetry.

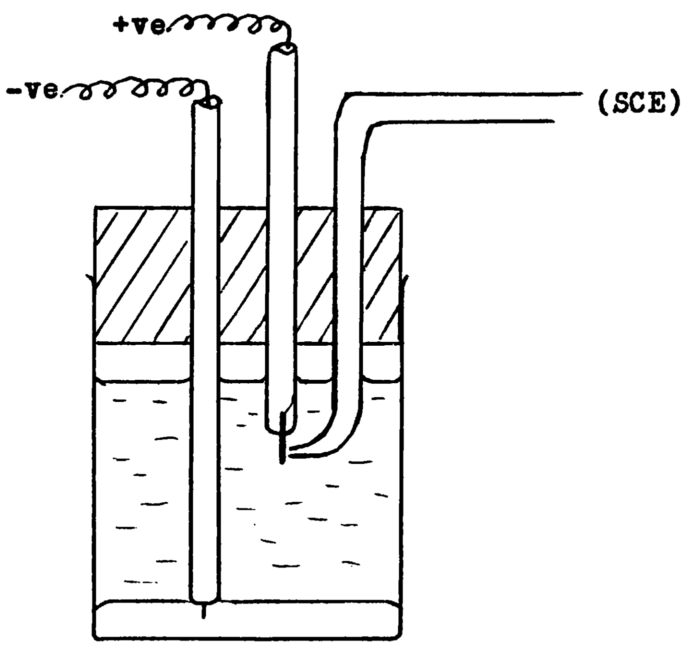
The main differences between conventional polarography and voltammetry are:

1. the time scale on which a voltage sweep is made,
2. the type of working electrode that may be used.

Commonly employed voltage sweep rates in voltammetry range from 10mV/sec - 100v/sec whereas polarography normally employs 1v/300sec. The electrodes used in voltammetry can be the same as in the preparative experiment, and thus platinum bead, or wire microelectrodes are often employed. In other respects voltammetry resembles polarography: the electrode potential is linearly swept while the current through the working electrode is monitored; the results are displayed on either an 'X-Y' plotter or an oscilloscope. A simple one compartment, three electrode cell may be used for voltammetry (Figure 9), but the precautions of an inert atmosphere and anhydrous conditions must be observed.

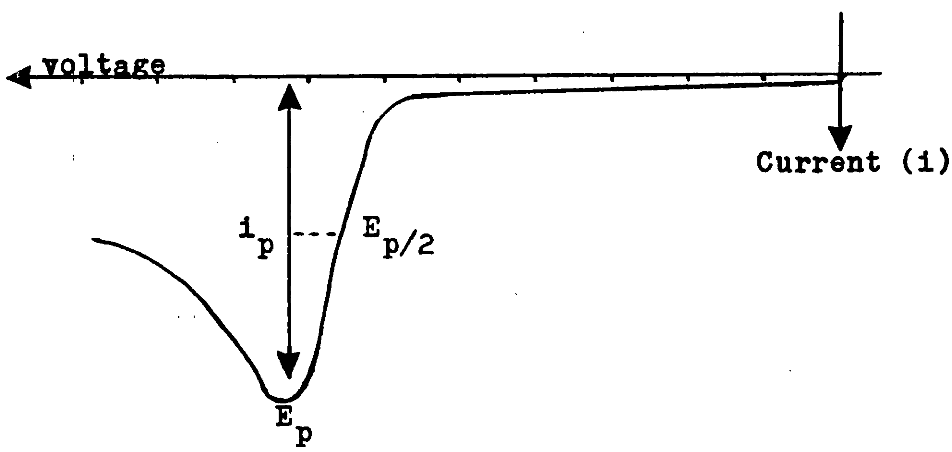
The higher scan rates used, cause voltammograms to assume a different shape to those of typical polarograms. Consider an electroactive species which undergoes a reversible one electron oxidation. As the electrode potential increases, current begins to flow when the substrate commences to be oxidized. Then the current rapidly increases until all the

Figure 9



electroactive species around the electrode is consumed and the diffusion supply of substrate is exceeded, at which point, the current begins to fall. This gives rise to an oxidation peak (Figure 10), inflexion (E_p) arises where the concentration of substrate is zero; the maximum current (i_p) simply being proportional to the peak height.

Figure 10



The peak potential of a reversible oxidation in relation to the half wave potential of a reversible polarographic wave is given by equation 5.

$$E_p = E_{\frac{1}{2}} - \frac{0.029}{n} \text{ V} \qquad (5)$$

The half peak potential ($E_{p/2}$) for a reversible oxidation is also well defined (equation 6) and normally reversible peaks are relatively sharp extending only over 0.12v for a one electron oxidation.

$$E_p - E_{p/2} = \frac{0.057}{n} \text{ V} \qquad (6)$$

Furthermore, the peak potentials of a reversible oxidation peak are independent of scan speed[39],this statement, however, does not hold for an irreversible oxidation[40] and thus it is a useful criterion for establishing reversibility. The peak current (i_p) for a reversible electron transfer has been derived mathematically by Randles[41] and Sevcik[42] in terms of equation (7) which forms the foundation stone of many mechanistic interpretations of electrode reactions based on current-potential relationships.

$$i_p = k\, n^{3/2}\, A.D^{1/2}.C.V^{1/2} \qquad (7)$$

k = Randles-Sevcik constant

D = Diffusion coefficient

V = Scan speed

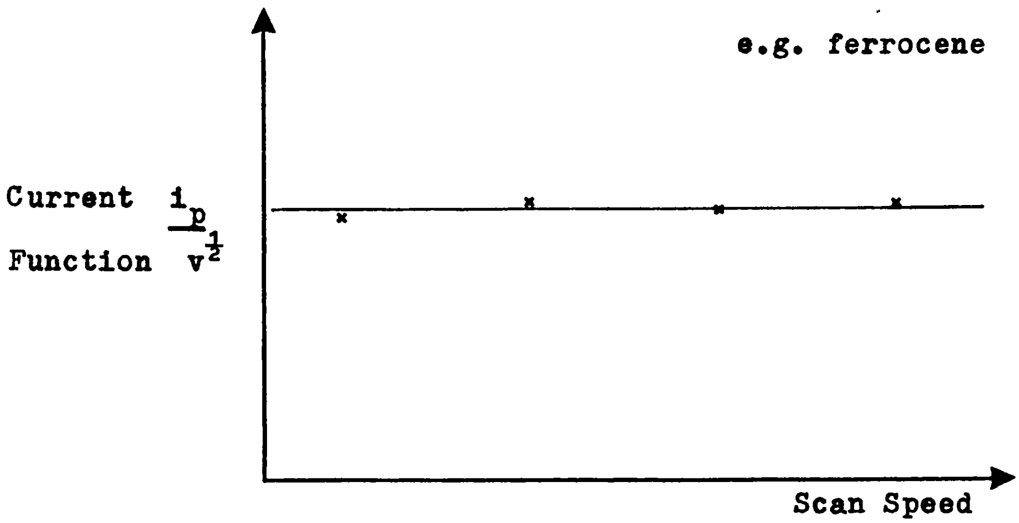
n = Number of electrons

C = Concentration of substrate

A = Area of electrode

For example, if all the variables in equation (7) are held constant, except for the scan speed (this is not difficult in practice), then the peak current becomes proportional to the square root of the scan speed. Thus the plot of peak current against square root of scan speed (current function) should result in a straight line for a reversible process. (Figure 11).

Figure 11



Clearly this ideal relationship is not always observed and curves result; Nicholson and Shain[43,44] describe such deviations and, depending upon the form of the curve, predict the nature of the electrode process (see page 64).

Equation (8) gives the peak current for an irreversible wave as derived by Delahay[45]. Qualitatively, irreversible oxidation peaks tend to be broader than their reversible counterparts and move to more anodic potentials as the scan speed is increased:

$$i_p = kn\ (\alpha N_a)^{\frac{1}{2}}\ A.\ D^{\frac{1}{2}}.\ C.\ v^{\frac{1}{2}} \qquad (8)$$

α = transfer coefficient (normally between 0.3 and 0.7)

Na = number of electrons in the rate controlling step.

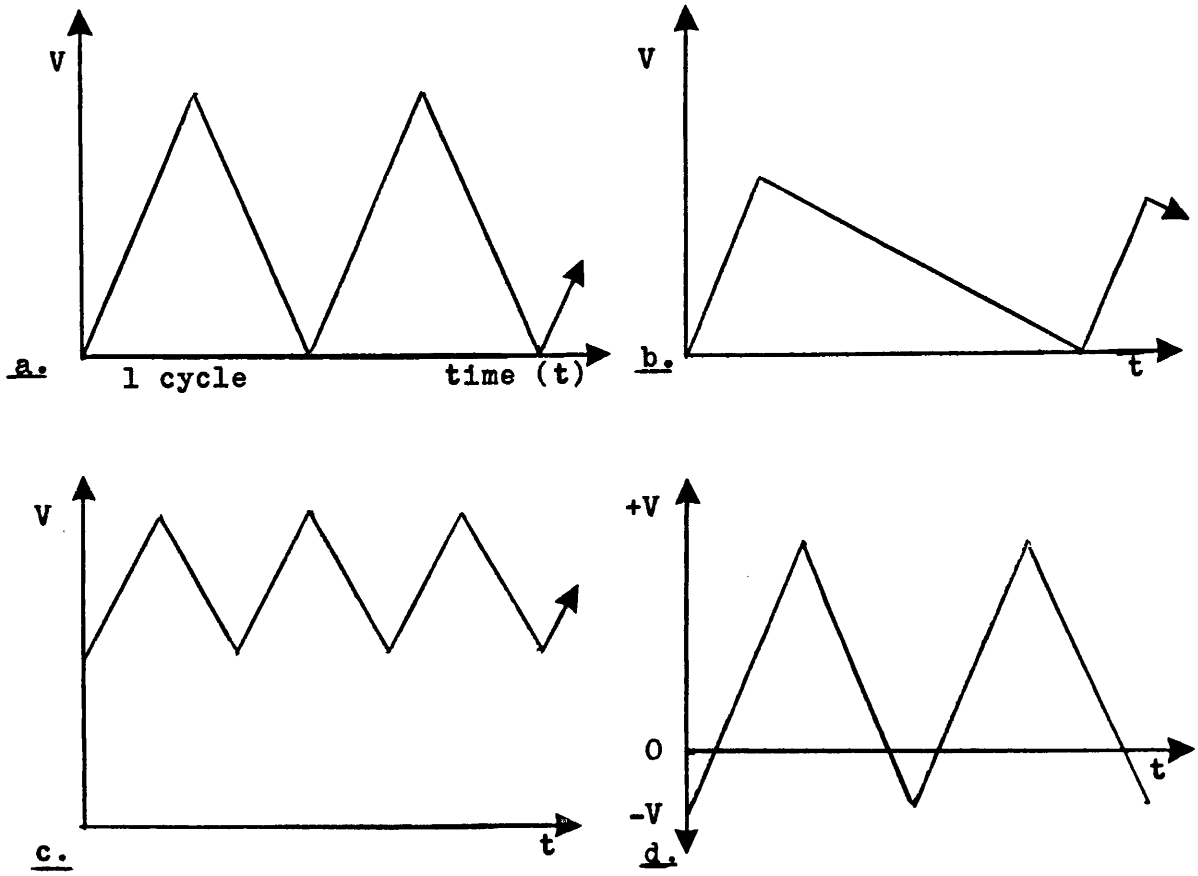
The term α in equation (8) simply determines the fraction of the electrode potential that assists the forward reaction, and the term αN_a may be evaluated by measuring the difference between peak and half peak potentials with the use of equation (9)[46].

$$E_p - E_{p/2} = -1.857 \left(\frac{0.026}{\alpha N_a} \right) \tag{9}$$

A slightly extended and more complicated technique than linear scan voltammetry is triangular wave or cyclic voltammetry. In cyclic voltammetry a triangular or sawtooth waveform is applied to the working electrode, the waveform need not necessarily be symmetrical (Figure 12).

<u>Figure 12</u>

Various waveforms applicable to cyclic voltammetric analysis techniques.



Cyclic voltammograms are again plotted on a suitable X-Y recorder with the X-ordinate representing the electrode potential. The technique seems to be used in two distinct modes of operation:

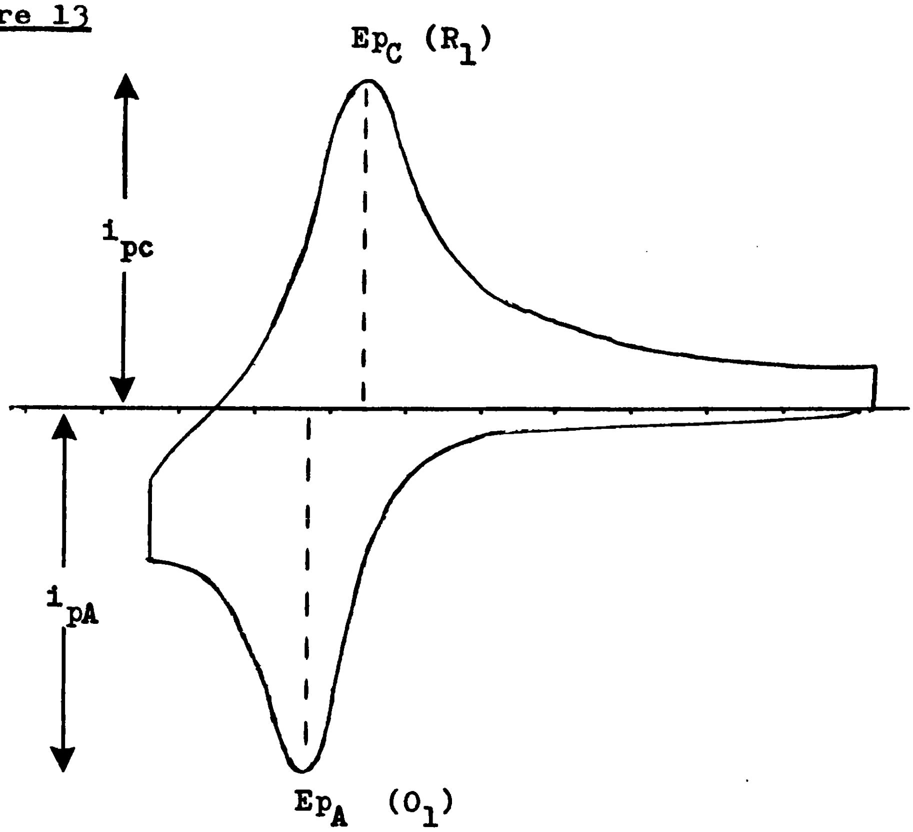
1. Single sweep techniques, where sufficient time elapses between scans for the initial concentrations of substrate to be regained in the diffusion layer of the electrode.

2. Multisweep techniques, where a continuous sawtooth waveform is applied to the electrode. Due to the secondary chemical processes which normally occur in organic electrode reactions, the first and second sweeps are often quite different, with steady state conditions normally being reached after five to ten cycles.

For the single sweep technique the current potential relationships are the same as for linear scan voltammetry, with the added advantage that the reverse scan can simplify considerably the interpretation of electrode mechanisms. Consider again the example of a substrate that undergoes a one electron reversible electron transfer (oxidation). As with linear scan voltammetry, the electrode potential is linearly swept and as the oxidation potential of the substrate is reached, current begins to flow, giving rise to an oxidation peak (O_1)(see figure 13). At a predetermined value, the voltage sweep is reversed (referred to as the switching potential) and current flows in the reverse direction. At this point the electrode is surrounded by oxidized species, and as the electrode potential falls the species is reduced, affording the reduction peak (R_1).

Clearly, for a truly reversible reaction, the ratio of the peak currents ($\frac{ipc}{ipa}$) will be unity and just as the anodic peak (O_1) is 28mV more anodic than the polarographic half-wave potential ($E_{\frac{1}{2}}$), the reductive peak (R_1) is similarly

Figure 13

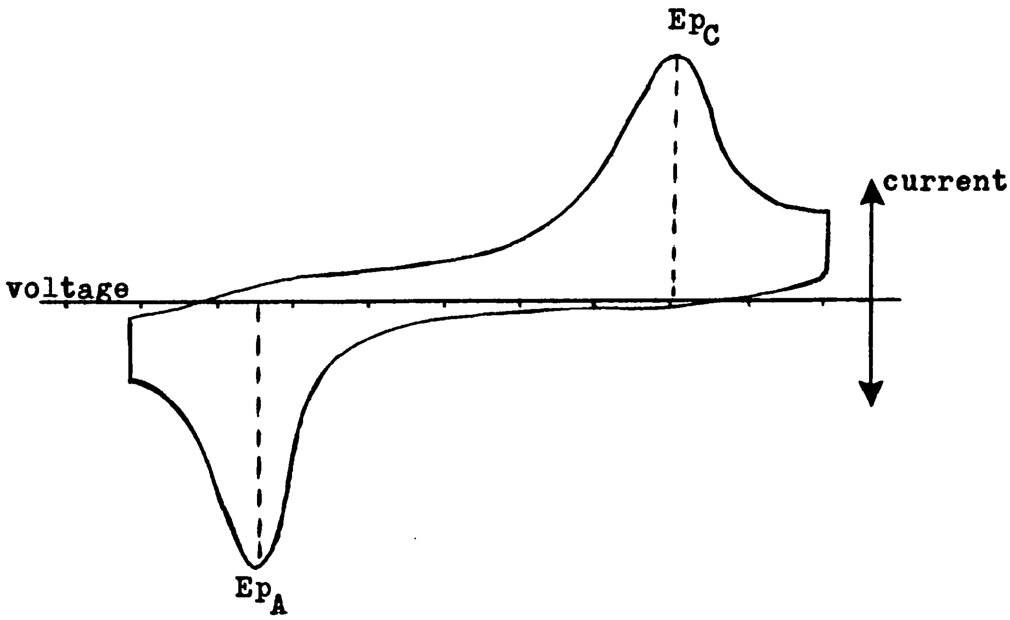


displaced in a cathodic direction. Thus for a "redox" couple in cyclic voltammetry, the difference between cathodic and anodic peak potentials (Ep_A-Ep_C) for a one electron reaction is equal to 56mV, this being an extremely useful criterion for judging reversibility. The small "flyback" peaks at the end of each sweep (figure 13) are caused by discharge of twice the charging current from the electrical double layer[47] and hence are non-Faradiac processes .

A second general example is of a slow charge transfer irreversible oxidation without an accompanying chemical reaction (figure 14). Generally speaking, peaks will be broader at higher scan speeds and oxidative peaks will become progressively more anodic on increasing the scan speed. Reductive peaks will be displaced equally, but in a cathodic direction. Clearly the distincion made between reversible and irreversible processes is artificial and only based on the rate of charge transfer, which can be affected by both background electrolyte and electrode material.

Figure 14

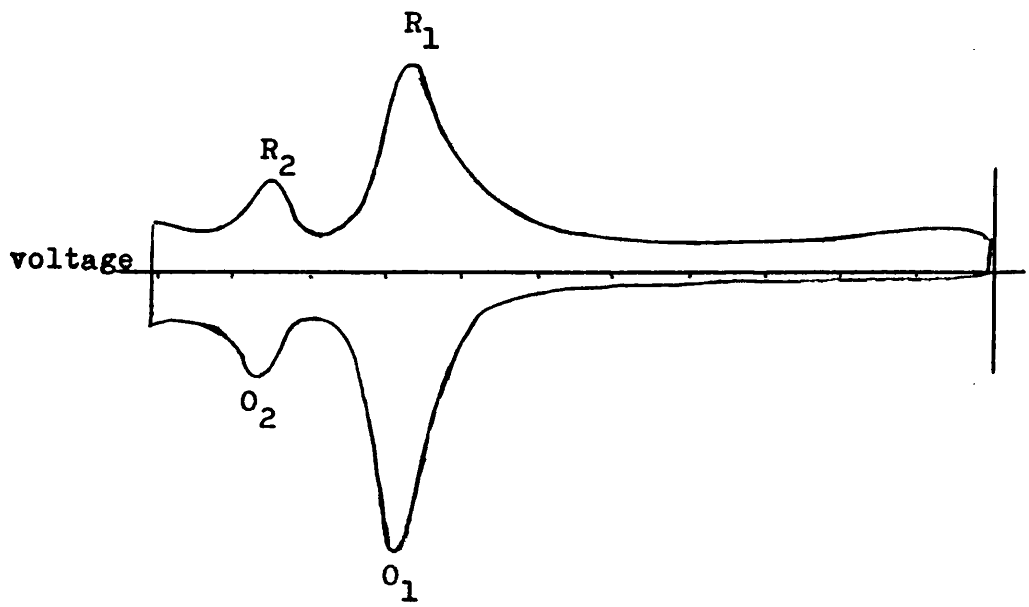
$Ep_a - Ep_c \propto \frac{1}{V^{1/2}}$



Nicholson has described methods for evaluating rate constants of electron transfers from peak separations at varying scan speeds[44], this description is of little relevance to the theme of this thesis.

The third general case is that of a reversible electron transfer with an associated chemical reaction (figure 15). Here, oxidation of the compound at O_1 produces an oxidized species which is sufficiently reactive to form a product having an oxidation potential O_2. If complete conversion of the oxidized substrate has not been effected by the time the voltage sweep has returned to its reduction potential, then the reductive peak R_1 will be observed. If, however, the oxidized species undergoes a fast chemical reaction (compared to the time scale of the voltammetric sweep) then R_1 will be absent. In any event, the reductive peak R_1 will be less

Figure 15



intense than O_1, but on the second and subsequent scans it is likely that O_1 will be very much reduced in intensity. We have made two assumptions in proposing this case, firstly, that the chemical product has a higher oxidation potential than the starting substrate, and that it forms a stable redox couple (O_2-R_2). Rarely are these assumptions strictly observed in practice, often the chemical product is oxidized close to, or below, the potential of the starting material[48] and on oxidation, undergoes further chemical reactions. Indeed this is probably one of the main contributory factors which cause low yields in some coupling reactions[49].

Lastly, caution must be exercised in the interpretation of cyclic voltammetric data when direct comparisons are made with the results from preparative experiments. Normally, controlled oxidations are conducted at fairly low current densities in the region of the substrates first oxidation potential. Therefore, a complete potential excursion revealing all the oxidative peaks of the substrate may not only supply superfluous information, but cause electrode reactions to occur that are not possible in the preparative cell. To this end, potential scan cyclic voltammetry (PSCV) has developed[50], this technique is discussed later (page 78).

Factors affecting oxidation potentials

In all of the work presented in this thesis, the primary electrochemical process is the removal of electrons from an aryl nucleus, therefore a brief consideration of the major factors influencing this step is now relevant. Clearly, electron donating groups will not only reduce the first oxidation potential, but will stabilize the resultant positively charged species. Electron withdrawing groups will have the reverse effect (cf. Table 1).

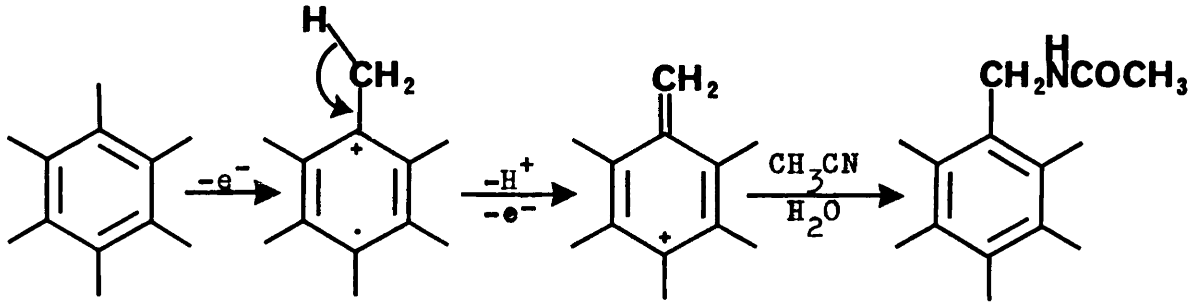
Table 1

Compound	$E_{1/2}$ vs SCE (acetonitrile)
Benzene*	2.08
Anisole	1.76
Mesitylene*	1.51
1, 4-Dimethoxybenzene	1.34
1, 2, 4, 5-Tetramethoxybenzene	0.81

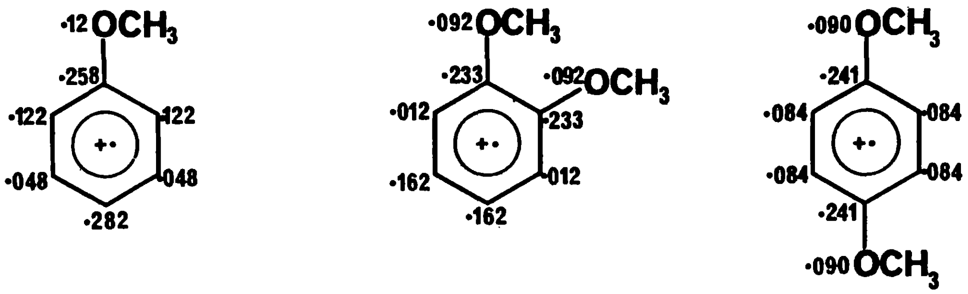
* With Ag/Ag^+ (0.1N) reference electrode

Thus it may be seen that stabilization of the induced radical cation is not only favoured by conjugation (as in the methoxybenzenes) but also by hyperconjugation.

The ability of methylbenzenes to lose a proton on oxidation from the methyl group is well known; thus, the anodic oxidation of hexamethylbenzene in acetonitrile results in the formation of pentamethylbenzylacetamide[51], the reaction is believed to proceed by a stepwise E.C.E. process.



The presence of electron donating substituents may well lower the oxidation potential of the aryl nucleus, but the reactivity also depends to a large extent on the positions of substitution. Thus the reactivity of the 1, 2-dimethoxybenzene cation radical in acetonitrile is considerably more than that of the 1, 4-dimethoxbenzene cation radical as demonstrated by cyclic voltammetry; the latter forms a stable redox couple[52]. Zweig has studied the electron spin resonance spectra of various methoxybenzenes[53,54] and his work has provided important information on the electron distribution and hence the preferred modes of coupling of the corresponding radical cations.



It may be seen that the veratryl cation radical has relatively high spin densities on the carbon atoms para to the methoxy functions, and as these positions are sterically unhindered, coupling reactions at these sites are preferred and readily occur. However, the 1, 4-dimethoxybenzene cation radical has the highest spin densities at the most hindered positions 1 and 4, a fact which accounts for its relative stability. The cation radical of anisole, like that of veratrole, has a high spin density para to the methoxy function and preparative anodic oxidations show that a para coupled dimer is the major product when the ether is oxidised in the absence of nucleophiles[49].

Electron removal occurs from the highest energy filled molecular orbital[55]. It is not surprising therefore, that good correlation has been found for the methoxybenzenes between half wave oxidation potentials, ionization potentials and the Hückel predicted energies of the highest filled molecular orbitals[53,54].

Footnote: Because of difficulties in using 'Letraset', throughout this work the normal convention of dotted circles to denote delocalised systems containing less than six electrons is not followed.

The mechanism of oxidative coupling

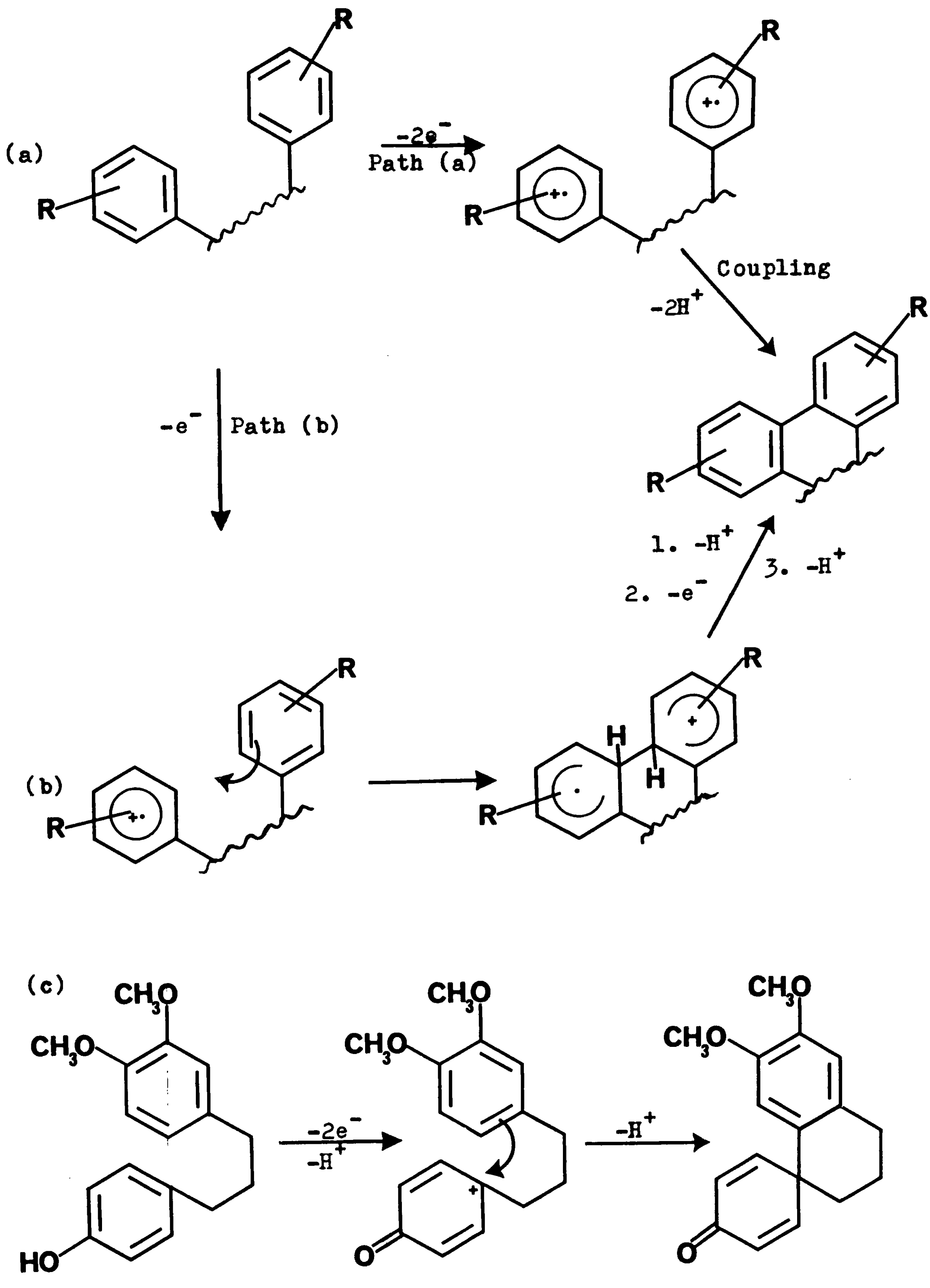
The exact sequence of events in electrooxidative coupling reactions leading to para-para coupled products has been the point of some conjecture. Three different mechanisms of coupling have been proposed[49,56,57], these are outlined in Scheme 2.

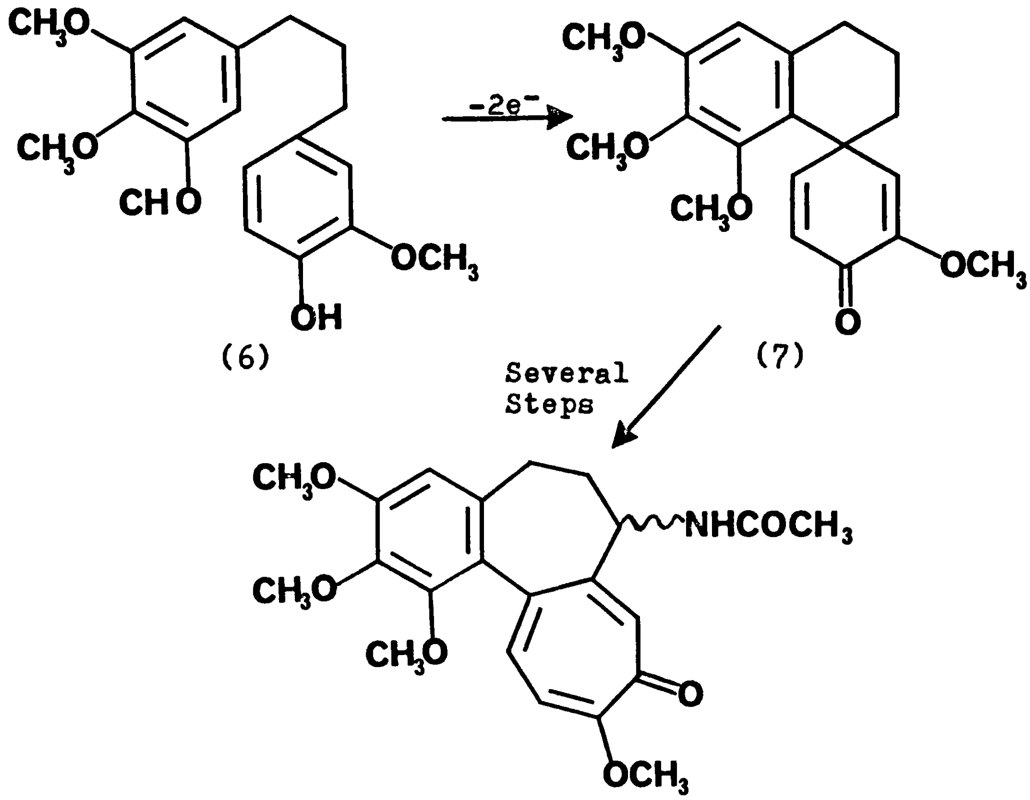
The first two routes 'a' and 'b' have been forwarded by Parker[49] and Nyberg[56] while scheme 2c represents a specific reaction, although it has some general applicability to the coupling of phenols to methoxylated aryl systems.

At first sight, it seems that the approach of two positively charged aryl nuclei (scheme 2a) is unlikely, but inspection of the literature shows that this type of reaction is in fact presumed to be quite common[49]. Thus there is a weight of evidence to indicate that if the two aryl nuclei have similar oxidation potentials then scheme (a) is the major reaction pathway, although formation of products via scheme (b) cannot be entirely precluded.

The third scheme (c) has practical implications to electroorganic synthesis. The facile loss of the phenolic proton forces coupling para to the hydroxyl function, even when other electron donating groups are present. Kotani[58] has used this principle in the synthesis of (±) colchicine, thus coupling to the more hindered position of the 3-methoxy-4-hydroxyphenyl moiety of the diaryl propane (6) leads to the formation of the desired dienone (7).

Scheme 2

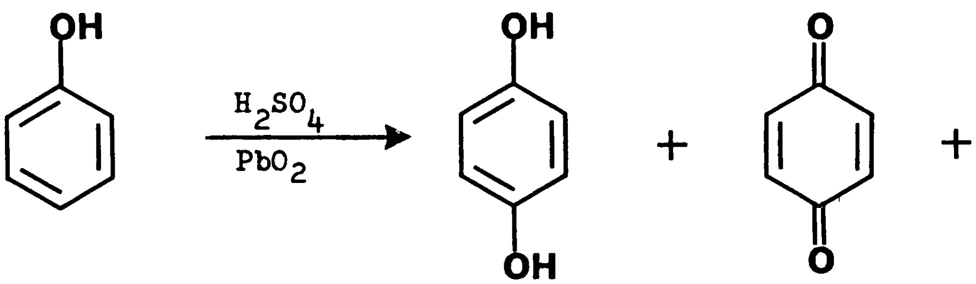

(a)
R
R
-2e⁻
Path (a)
R
R
Coupling
-2H⁺
R
R
-e⁻
Path (b)
1. -H⁺
2. -e⁻
3. -H⁺
(b)
R
R
R
R
H
H
(c)
CH3O
CH3O
HO
-2e⁻
-H⁺
CH3O
CH3O
O
-H⁺
CH3O
CH3O
O

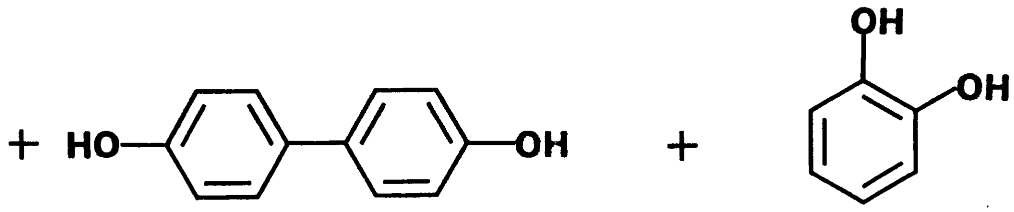


(±) Colchicine

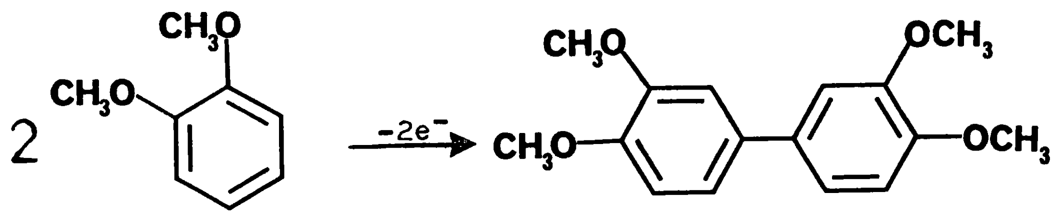
A brief literature review of anodic coupling reactions.

Some the earliest aryl-aryl coupling reactions carried out electrochemically, were upon phenols, using a lead dioxide anode and a dilute sulphuric acid electrolyte. Fichter pioneered most of this early work, employing extremely basic electrochemical equipment. One of his first experiments was the oxidation of phenol to obtain the following products[59].

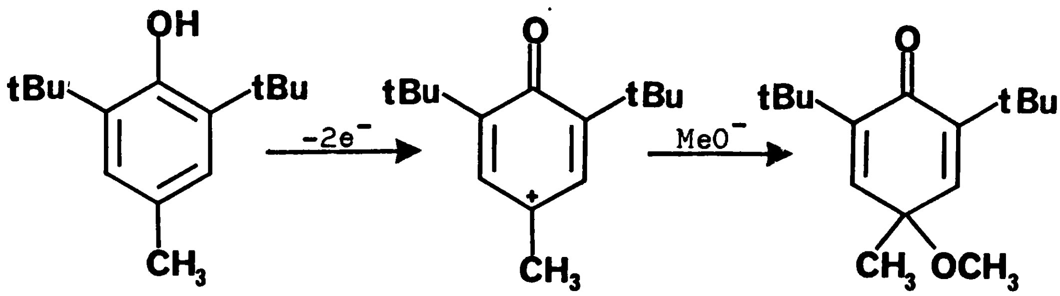




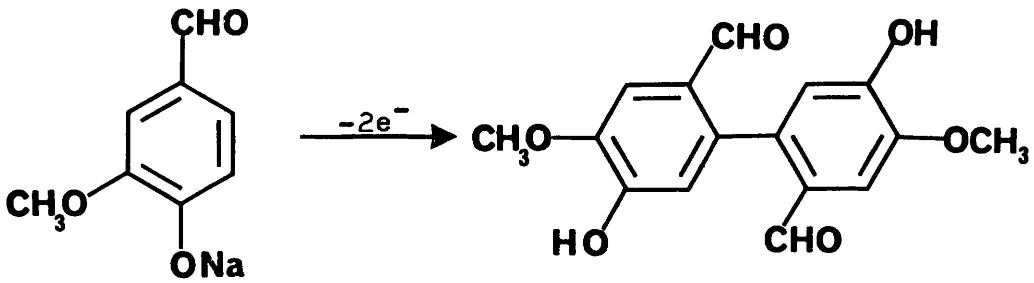
This serves as a useful reminder of the multiplicity of reactions that may occur at the anode (subsequently, however, Covitz has developed this reaction to afford hydroquinone in over 90% yield[60], by control of the working potential). Later work by Fichter on simple methoxybenzenes, using either a platinum or lead dioxide anode, gave para-para coupled products in moderate yield[61], thus 1, 2-dimethoxybenzene yields 3, 3', 4, 4'-tetramethoxybiphenyl:



After this early work, there followed a long period of relative inactivity until, Pearl et al. studied the oxidation of phenols with the aid of voltammetry. It became apparent that two different oxidative pathways for phenols could occur[62], firstly a one electron oxidation of the phenoxide anion to give a radical, or a two electron oxidation of the neutral species to give a phenoxonium ion. The products of the reaction depended upon which pathway was followed: thus the formation of a radical normally resulted in coupled products[62] whereas an intermediate phenoxonium ion gave products derived from nucleophilic attack[62]. For example, the oxidation of 2, 6-di-t-butyl-p-cresol in the presence of methanol resulted in the formation of the quinone (8), while oxidation of vanillin salts gave the dimer (9)[62].



(8)

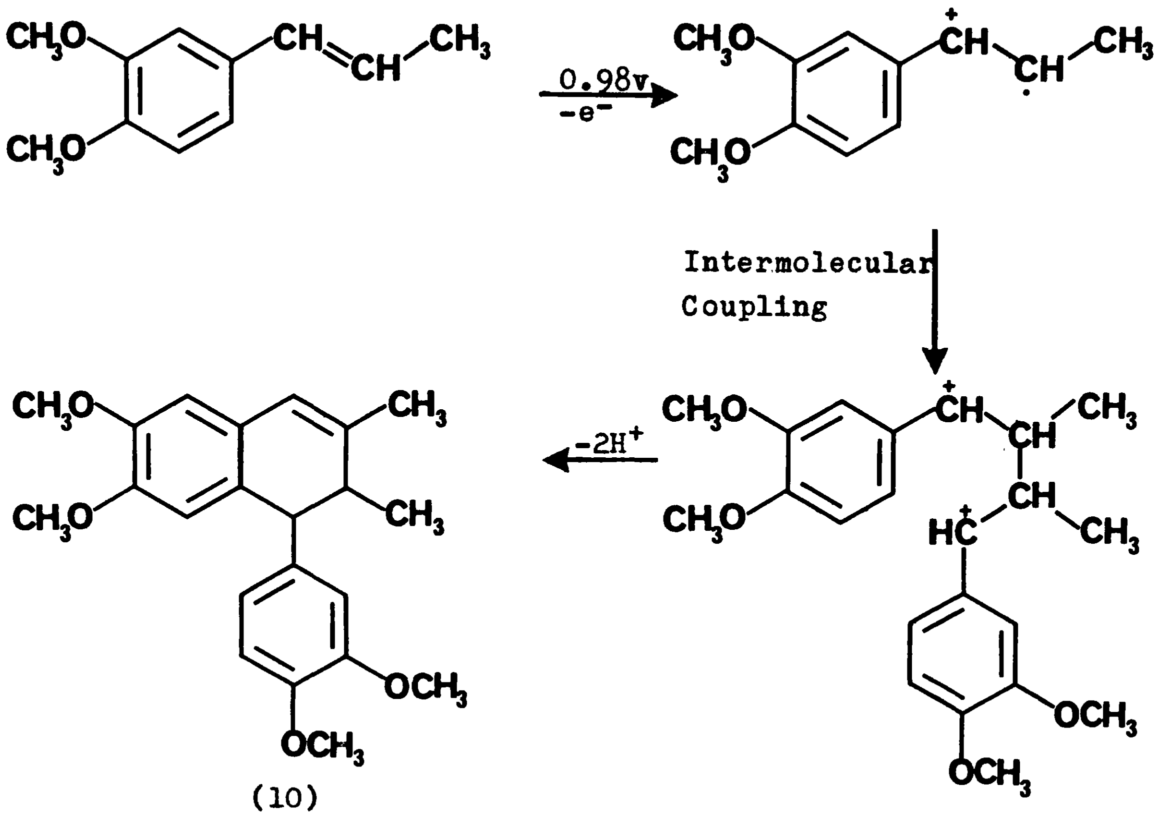


(9)

More interestingly (from our viewpoint) Pearl and O'Connor[63] conducted a controlled potential anodic oxidation on 3, 4-dimethoxypropenylbenzene in acetonitrile solvent and sodium perchlorate supporting electrolyte. They obtained the dehydrodimer (10) by the mechanism outlined in Scheme 3.

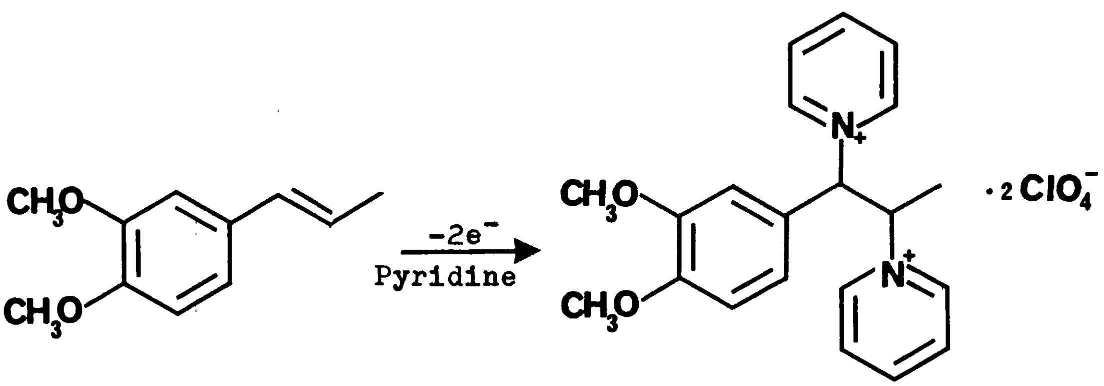
They also reported that pyridine prevented the formation of (10). Later work by Sainsbury showed that two mol. of pyridine add to 3, 4-dimethoxyphenylpropenyl benzene to give the dipyridinium perchlorate salt[64].

Scheme 3

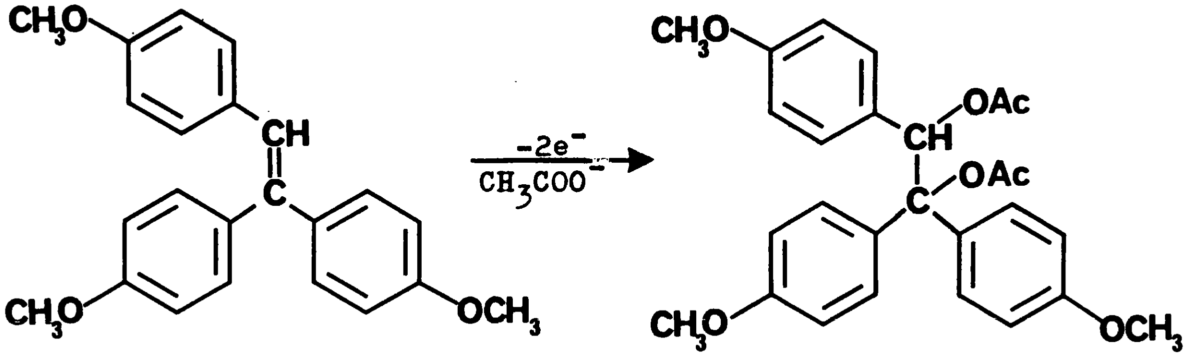


(10)

The formation of di- and even tripyridinium salts from the anodic oxidation of α-arylolefins seems to be a reaction of general applicability[65], and it appears that most nucleophiles react in a similar way to that of pyridine.



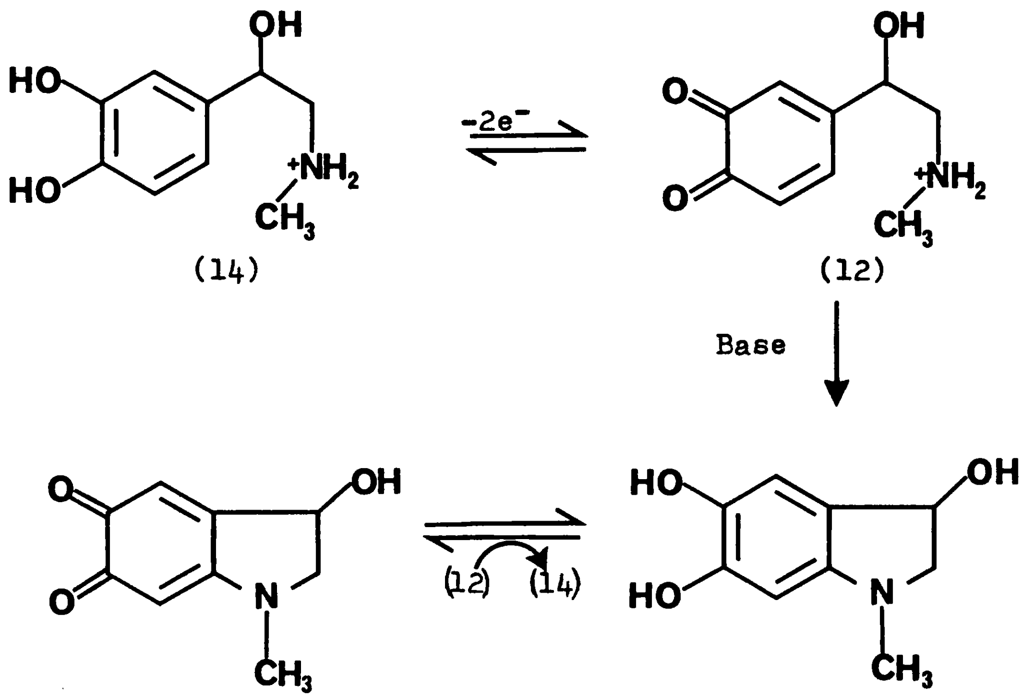
Thus, when tris (p-methoxyphenyl) ethylene is oxidized in the presence of acetate ion, the diacetate (11) is formed.



(11)

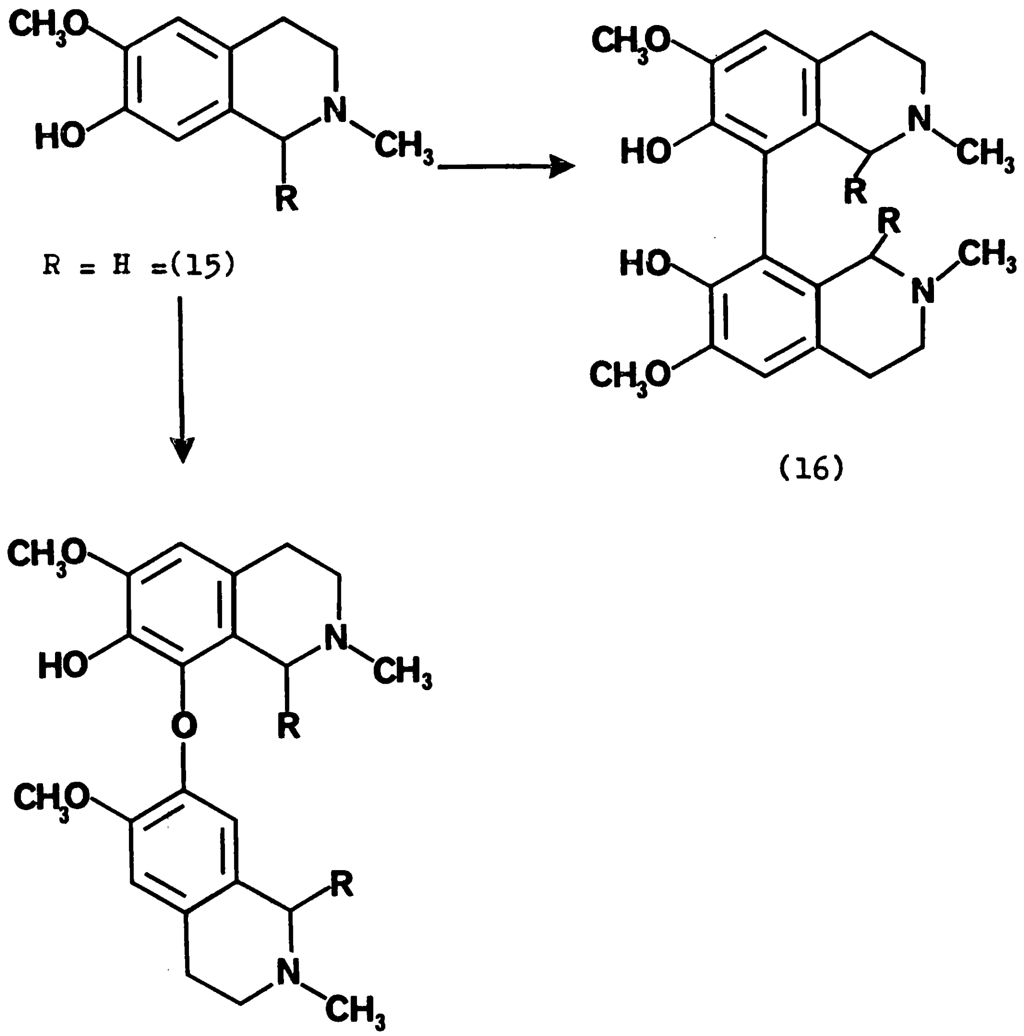
This type of reaction should be potentially useful in the synthesis of lignan type structures, but so far this goal has not been realized.

Adams has studied the anodic oxidation of the biologically important catecholamines[67]. Thus, the anodic oxidation of adrenaline gives the intermediate quinone (12) which then undergoes a 1, 4-addition reaction to the catechol (13)[68].



(14) (12) (13)

This interesting reaction receives further attention on page 148 . In recent years other natural products particularly those based upon the isoquinoline system have received the attentions of electro-organic chemists. Pioneering studies were conducted by Bobbitt and his co-workers on the anodic oxidation of corypalline (15)[69]. This gave the dimer (16) in good yield.

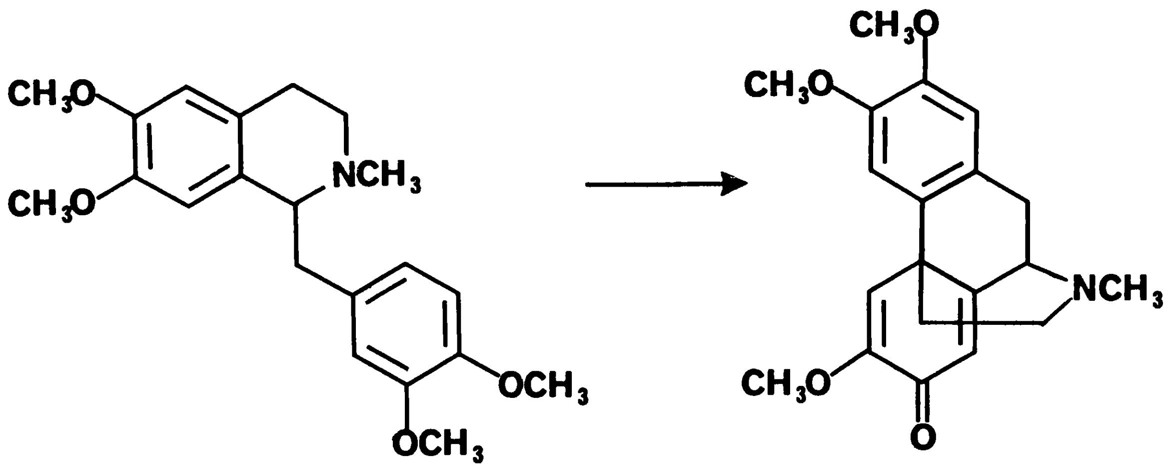


R = H =(15)

(16)

(17)

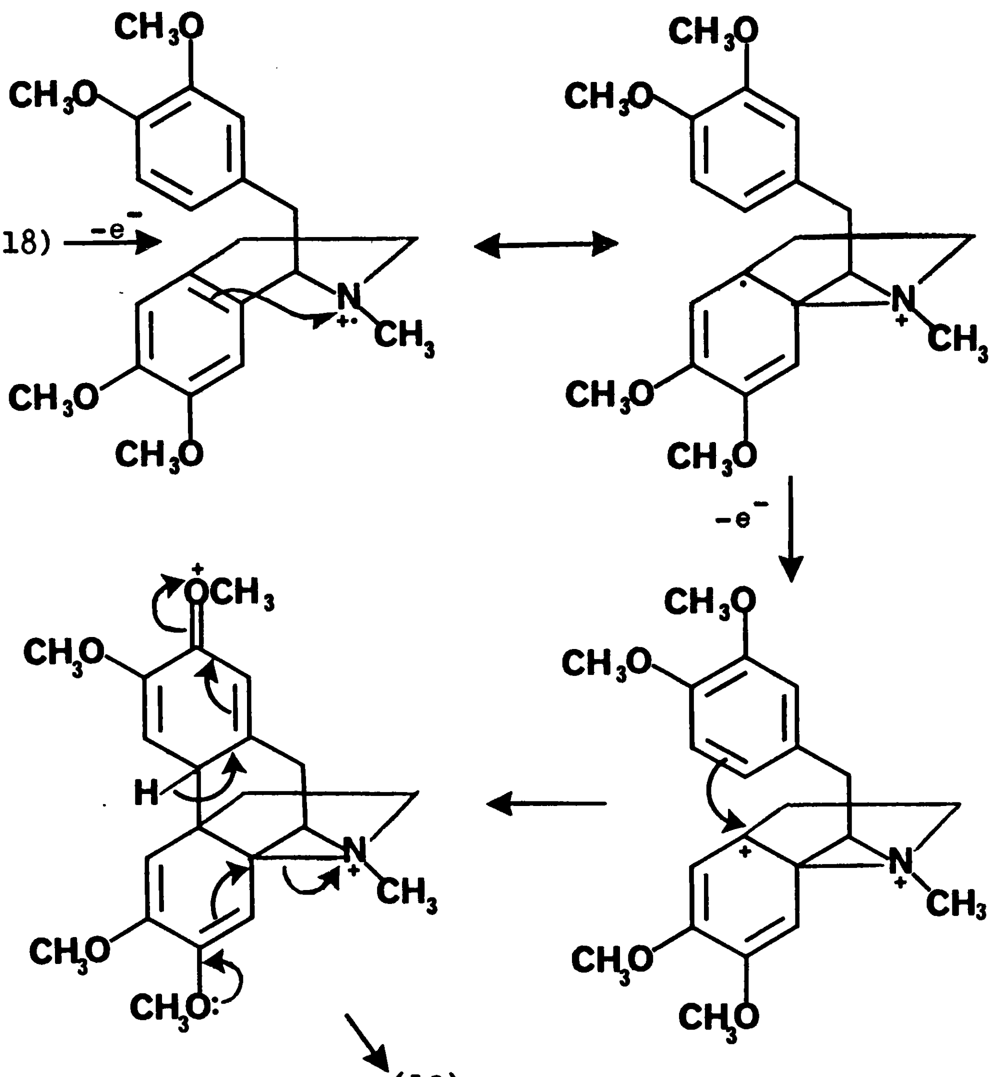
Later studies examined the effect of replacing the hydrogen atom R in (15) with a methyl or ethyl group. When either of these functions were present, the yield of (16) was minimal and carbon to oxygen coupling predominated giving rise to the structure (17). Subsequently, Stermitz and Miller studied the intramolecular coupling of the 1-benzylisoquinolines to give morphinandienones[70]. The electrooxidation of ($\pm$)-laudanosine (18) at 1.10v (Ag/Ag^+) in an acetonitrile lithium perchlorate electrolyte gave ($\pm$) O-methylflavinantine (19) in 52% yield. They proposed that the mechanism for this process



(18) (19)

involved a simple diradical-dication coupling of the two aryl nuclei, and ignored the fact that the first oxidation potential of (18) occurred at 0.63v[70], which must be attributed to oxidation of the nitrogen atom. Later they resolved this anomaly by proposing a mechanism which involves anchimeric assistance by the oxidized nitrogen aiding the formation of the dienone (19)[71]. The mechanism is validated by the fact that substantial amounts of (19) are produced at electrode potentials of 0.5v[71].

(18)

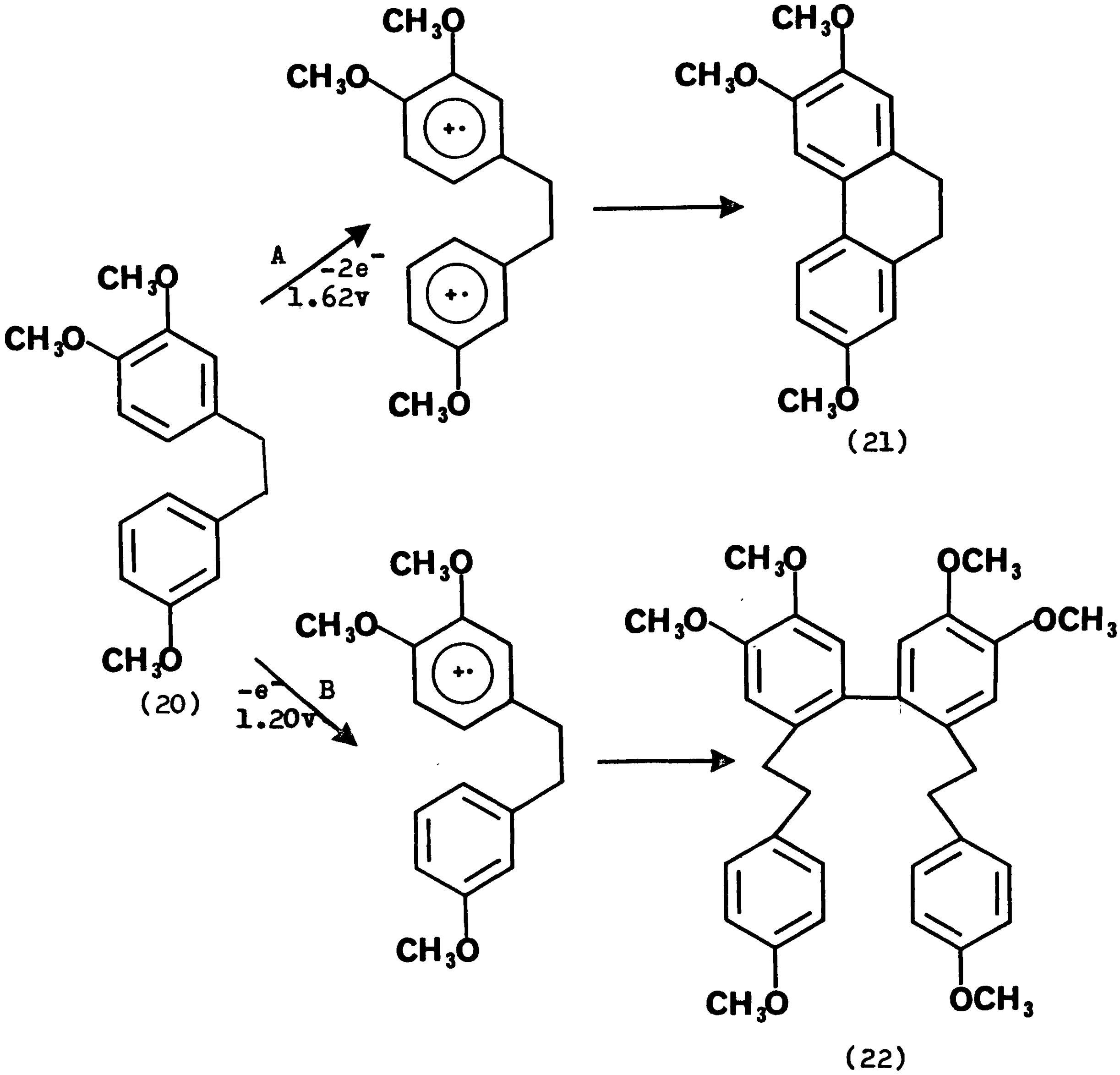


(19)

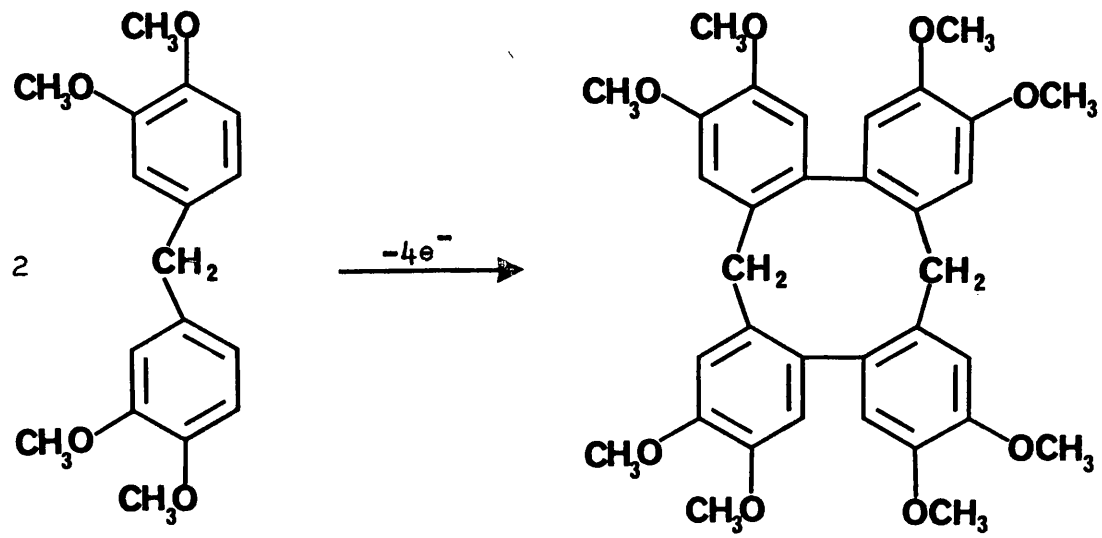
Kotani has also been active in the alkaloid field, and has synthesised both (±)-oxocrinine[72] and (±) colchicine[58] electrochemically (see pages 57 and 36).

Normally organic electrochemists show a preference towards either the synthetic applications of the method or a more theoretical mechanistic approach. Parker and his colleagues, however, have been active in both of these fields, regularly publishing details of useful syntheses accompanied by a mechanistic rationale based on cyclic voltammetric data.

Considerable work was carried out on the anodic oxidation of both symmetrical and unsymmetrical diarylalkanes for example, and a study made of the products obtained[49,57,53]. Attempts were made to categorize the modes of coupling that would occur, in terms of the alkane chain length,and aromatic substitution patterns[73]. Thus, the unsymmetrical bibenzyl (20) undergoes intramolecular coupling at high current densities,(Path A)to give the dihydrophenanthrene(2I)<u>via</u> the dication diradical[49]. However,at low current densities (Path B),only the veratryl unit is oxidized and hence the dimer (22) is formed.



The formation of large ring dimeric structures of type (22) were observed when the number of carbon atoms in the alkane link make intramolecular coupling unfavourable[74].



(22)

A considerable volume of literature is quoted in the discussion part of this thesis, when, and where its relevance is greatest. In order to minimize repetition, this section is therefore drawn to a close, but for a more complete appraisal of organic oxidative electrochemistry, several excellent texts are available[23,24,31].

Finally, mention should be made of the chemical reagents that may be used to effect non phenolic, oxidative aryl-aryl coupling. In the past few years there has been an upsurge in the use of such electron transfer reagents as vanadium oxyfluoride[75], thallium trifluoroacetate[76] and iron/D.M.F. complexes[58]. In many cases anodic coupling can be paralleled by the use of these chemical oxidants, which occasionally offer advantages in terms of yields of product and simplicity of use. However, in the end the anodic method must offer the greater degree of control (by judicious choice of the electrode potential) and, of course, greater understanding of the electrode reactions can be gleaned by the use of the electroanalytical instrumentation now available.

CHAPTER 1

The Anodic Oxidation of some simple Diarylalkyl Amides.

Introduction

Intramolecular oxidative aryl-aryl coupling can be achieved in several ways, but probably the best known is phenolic oxidation, which is, of course, fundamental to many biosynthetic pathways[1].

In the laboratory, phenolic coupling is usually replicated by the use of inorganic oxidants in alkaline media, but the manipulation of phenolate anions and poly-hydroxy compounds is always difficult and over oxidation is often a problem.

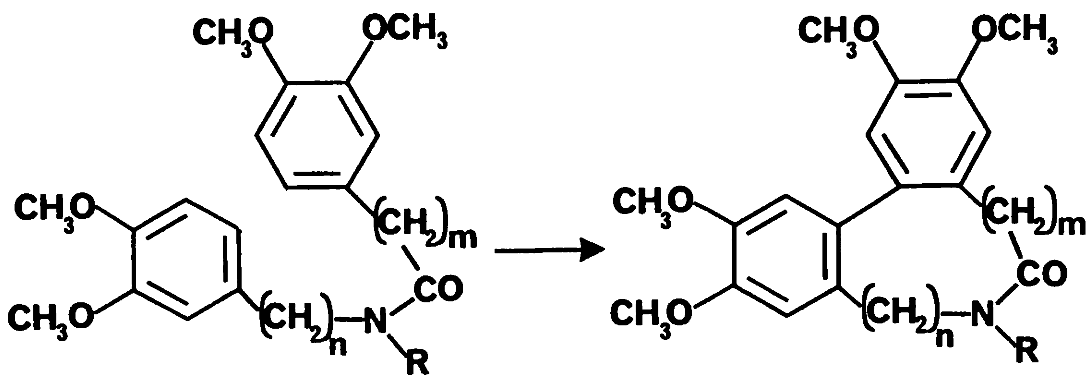
Alternative methods of joining two aryl nuclei include the Pschorr reaction and the photo-cyclization of stilbenes[2]. Often, however, the required starting materials are difficult to prepare and the methods cannot be described properly as direct.

Anodic oxidation on the other hand offers a simple and attractive route to biaryls using readily available substrates and a wide degree of selectivity through precise control of electrode potential. In principle such a process should have an established place in the armoury of the synthetic chemist and present no more trouble in its application than say the setting up of a high pressure catalytic hydrogen experiment. So far, however, anodic oxidation has not received much recognition, and the purpose of this work is to illustrate its application to the coupling of certain amides and esters. The results of the oxidation of simple secondary and tertiary aryl-alkyl carbamides are presented in the first section of this thesis.

The choice of substrates and targets was occasioned through the interest of the collaborating body, Allen and Hanbury's Research Limited, and centres around the synthesis of seven and eight membered lactams and lactones.

(i) <u>The synthesis of dibenzoazocines and dibenzoazopines</u>

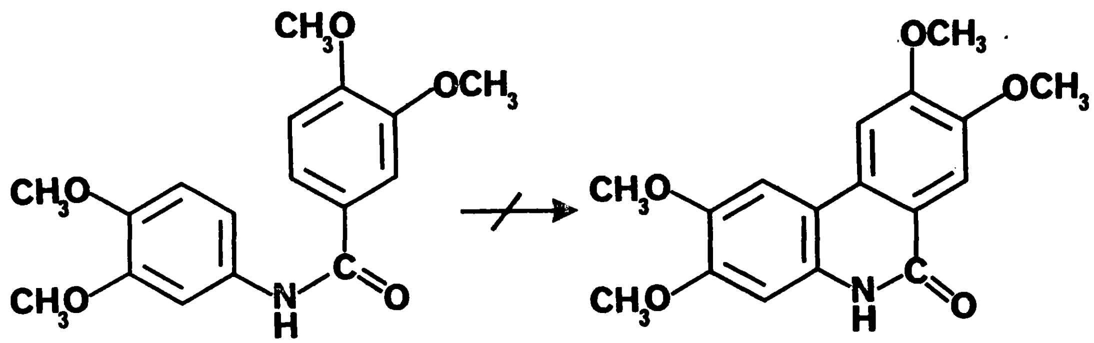
In general this investigation can be summarized by the following equation where n and m are zero or integers.



R = H or CH_3

Attempts to carry out simple <u>para</u>-<u>para</u> coupling of this type was beset from the beginning by unforseen difficulties and naturally this led to an investigation to determine why certain amides are poor substrates for electrolysis while others are easily oxidized. During the first stages of the work we did not have access to cyclic voltammetric instrumentation and some of our earlier conclusions regarding the mechanisms of oxidation were speculative. When such instrumentation became available it allowed a complete reappraisal of earlier studies and some anomalies were discovered. Since then, however, a self consistent theory has been sought and established.

At the start a thorough literature search revealed that no relevant work on the oxidation of aryl-alkylamides had been conducted and the only information of interest was an unpublished study by Sainsbury and Schinazi[3] of the electrolytic oxidation of N-(3, 4-dimethoxyphenyl)veratramide (I). Attempts to cyclize the amide (1) to the phenanthridine (2) were abandoned due to a rapid filming of the platinum gauze electrode with a black insulating tar.

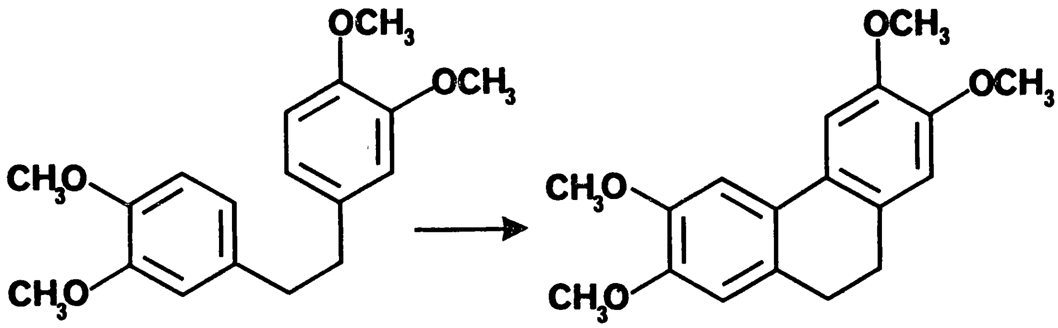


(1) (2)

In this case the film was at first barely visible to the naked eye, but within minutes of starting a preparative electrolysis the effective electrode area decreased and the cell current fell rapidly to zero.

Schinazi suggested that the failure to effect cyclisation could be attributed to the fact that the amide function adjoins both of the aryl rings and this imparts different oxidation potentials to them, and the benzoyl fragment is more difficult to oxidize than the anilino moiety. This being so, intermolecular coupling processes would predominate over intramolecular cyclisation and possibly lead to polymer formation.

This seemed a reasonable view for Parker reports[4] the successful anodic cyclisation of the bibenzyl (3) to the corresponding dihydrophenanthrene (4).



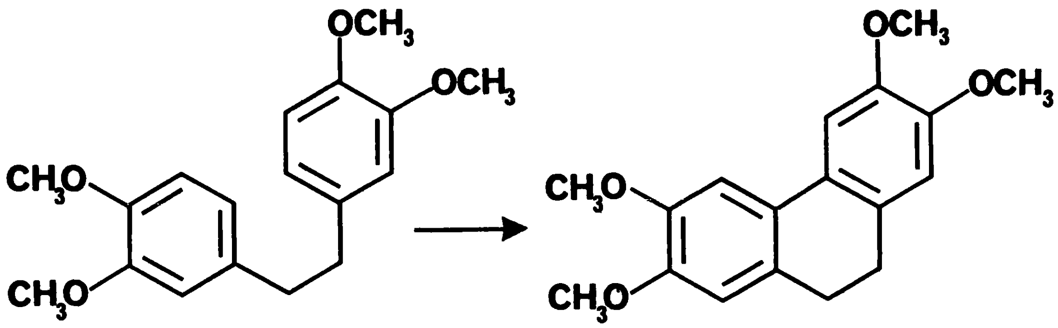
(3) (4)

In an attempt to design suitable substrates for anodic oxidation and subsequent intramolecular coupling, this factor was taken into account and we decided to isolate the amide function from the aryl rings by the insertion of methylene units on either side, but throughout the early study we retained 3, 4-dimethoxylated aryl ring system, principally because of the availability of starting materials, and its relatively low oxidation potential.

The first choice for anodic oxidation was N-homoveratroylveratrylamine[5] (6) as it would provide evidence for, or against, Schinazi's hypothesis. The simplest route to this amide seemed to be the reaction of veratrylamine with homoveratroyl chloride in the presence of base. Veratrylamine was made in a two step process from veratraldehyde.

possibly lead to polymer formation.

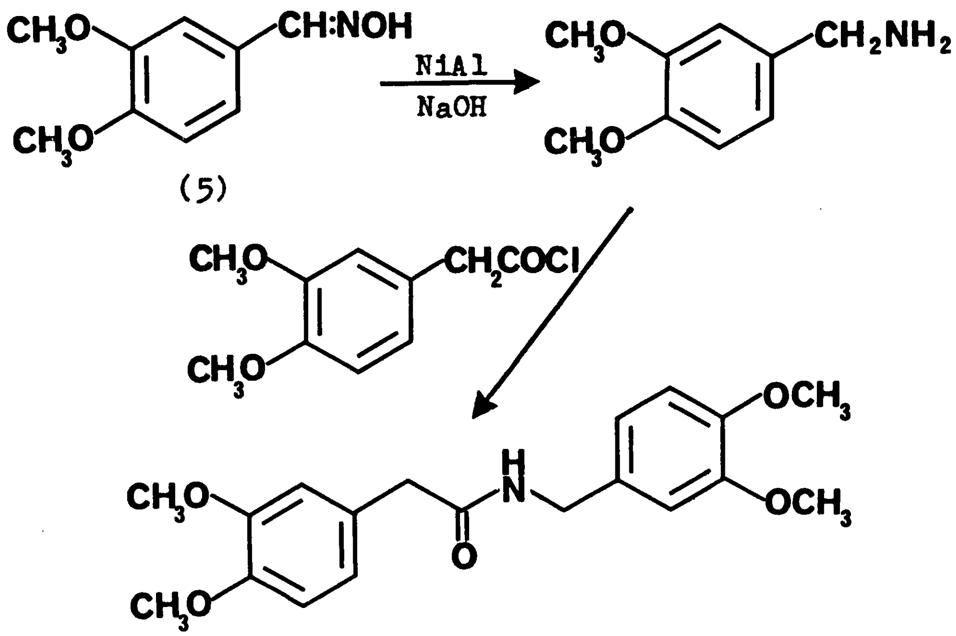
This seemed a reasonable view for Parker reports[4] the successful anodic cyclisation of the bibenzyl (3) to the corresponding dihydrophenanthrene (4).



(3) (4)

In an attempt to design suitable substrates for anodic oxidation and subsequent intramolecular coupling, this factor was taken into account and we decided to isolate the amide function from the aryl rings by the insertion of methylene units on either side, but throughout the early study we retained 3, 4-dimethoxylated aryl ring system, principally because of the availability of starting materials, and its relatively low oxidation potential.

The first choice for anodic oxidation was N-homoveratroylveratrylamine[5] (6) as it would provide evidence for, or against, Schinazi's hypothesis. The simplest route to this amide seemed to be the reaction of veratrylamine with homoveratroyl chloride in the presence of base. Veratrylamine was made in a two step process from veratraldehyde.



(5)

(6)

The reduction of veratraldoxime (5) with lithium aluminium hydride or sodium in ethanol gave a mixture of products rather than the pure amine, but Raney nickel and sodium hydroxide in ethanol affords an efficient reagent combination, and a high yield of desired product is obtained.

In older accounts the mechanism of this reaction is said to involve the formation of hydrogen which is then adsorbed on the surface of the freshly formed nickel. This then functions as an efficient hydrogenation catalyst. This, however, is likely to be a simplistic view and it is probable that a nickel aluminium couple is established; electron transfer from the cathode then effecting the reduction.

Homoveratroyl chloride[6] was obtained from homoveratric acid by the action of thionyl chloride in benzene. In this laboratory the acid chloride has a long and infamous history, tending to decompose extremely readily. Usually after distillation it is obtained as a red oil, but we noted when the whole reaction sequence was carried out in the dark the acid chloride was obtained as a white solid. This was relatively stable, but even so resinification occurred within a few days.

(ii) The anodic oxidation of N-homoveratroyl-veratrylamine (6)

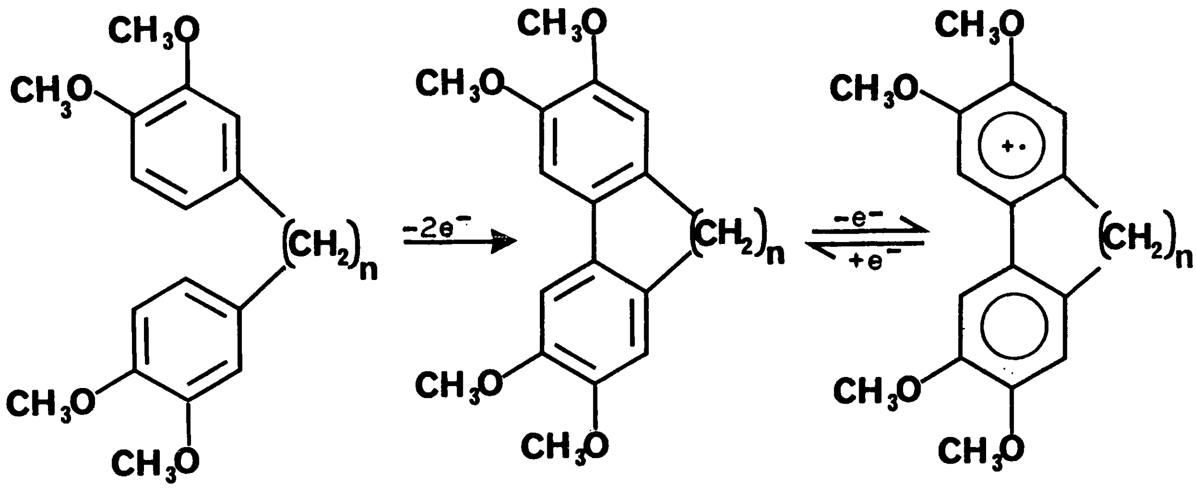
The anodic oxidation of the amide (6) was conducted in an *H*-type cell with dry acetonitrile and sodium perchlorate as supporting electrolyte. A flat platinum gauze served as the anode which was cleaned in warm concentrated nitric acid prior to use[7].

An initial anode potential of 1.15v (*vs*SCE) gave rise to a current density of $1mA/cm^2$ which quickly fell to zero, indicating that anode filming was occurring. In an attempt to maintain current flow, the electrode potential was pulsed to zero at regular intervals; this technique is often recommended in the literature[8] to overcome this type of problem, but unfortunately it had little effect on the course of our oxidation. The purpose of pulsing the electrode is to "reduce" unstable positively charged species which build up around the electrode during the course of an electrolysis. Once "reduced", presumably these can diffuse away from the anode and thereby alleviate electrode coating. Eventually after the electrode had been removed and its surface cleaned several times, the electrode potential stabilised at 1.20v (*vs*SCE) and the electrolysis was continued until two Faradays per gram mol. ($2Fmol^{-1}$) of current had been consumed. During the course of the oxidation the solution turned dark brown and work-up of the anolyte afforded a brown viscous oil.

Thin layer chromatography (SiO_2/chloroform) showed an almost continuous trail of unresolved products and as expected, column chromatography (SiO_2/$CHCl_3$-pet. ether gradient) failed to separate any single component.

During the coupling of aryl nuclei, protons are formed and we speculated that the changing acidity of the medium during the electrolysis might adversely affect the course of the reaction and so a second electrolysis of the amide was conducted in presence of anhydrous potassium carbonate[9], but again no products were isolated from the work-up.

Parker[10], during the successful anodic oxidation of some bis-(3, 4-dimethoxyphenyl)alkanes, employed a solution of dichloromethane and trifluoroacetic acid together with tetrabutylammonium tetrafluoroborate as supporting electrolyte, but using acetonitrile only poor yields of intramolecular products were obtained and electrode filming was often encountered. The reason for this difference was attributed to the stabilizing effect of trifluoroacetic acid on the cation radical product (8). The initially produced biaryl (7) apparently undergoes a one electron oxidation more readily than the starting diarylalkane and so reduction of (8) at the end of the three electron oxidation was necessary in order to obtain the coupled biphenyl (7).



(7) (8)

The apparent instability of cation radical (8) in acetonitrile was then adjudged to be the major reason for the poor yields, but the exact role of trifluoroacetic acid was not established.

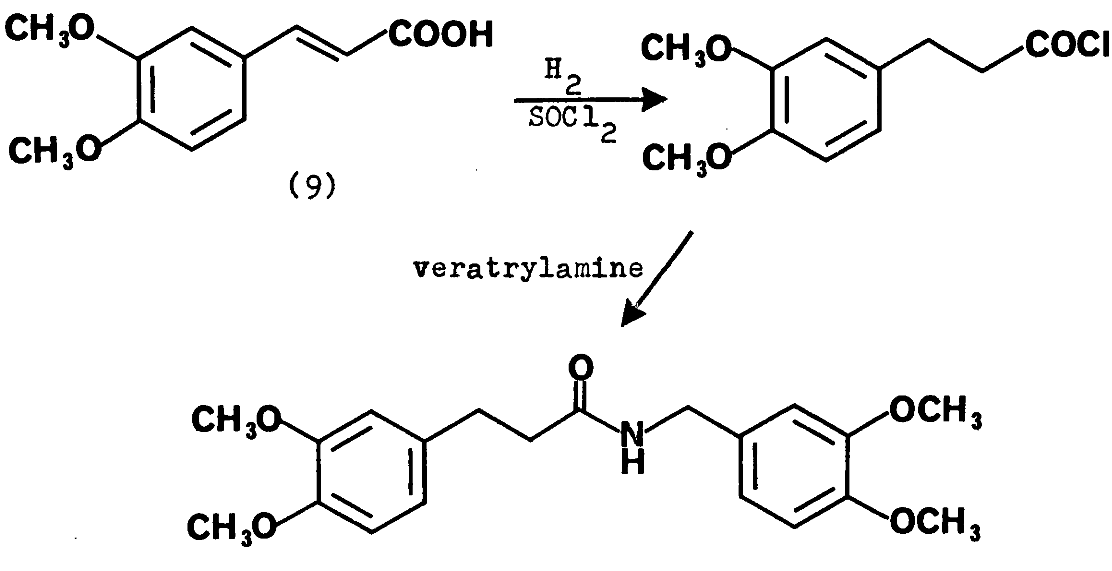
We anticipated that this could also be the reason for the failure of amide (6) to cyclize and so an anodic oxidation of this compound was conducted in this new electrolyte system. It was immediately apparent however, that some electrode filming was still occurring, but eventually a substantial current flow was maintained and after the passage of 3F mol^{-1} at 1.21v (vsSCE) the anode and cathode were short circuited and the anolyte stirred until no further reduction was observed. Work-up using column chromatography (SiO_2, ethyl acetate/pet. ether gradient) gave no resolvable products, and the use of chromatography was found to be the only effective means of separating the added tetrabutylammonium salt from the other organics present.

The failure of the amide (6) to undergo controlled oxidative coupling was puzzeling and tended to put Schinazi's hypothesis in doubt.

At this point we wondered whether the failure to effect cyclization could be due to some inherent factor associated with the electrochemical oxidation of secondary amides as such, and this led us to examine two other analogous substrates, the first of which was the homologue (10).

This compound was prepared very efficiently in the following manner.

β-(3, 4-Dimethoxyphenyl)propionic acid was formed by a Knovenagel reaction between malonic acid and veratraldehyde. A solution of the cinnamic acid (9) in dimethylformamide was hydrogenated over a palladium on charcoal catalyst to give the corresponding reduced acid. Conversion to the acid chloride in the usual way, followed by reaction with veratrylamine gave the amide (10) in good yield, (m.p. 129°-130°). The infra-red spectrum showed the characteristic amide stretching frequency of 1640 cm^{-1}.



(9)

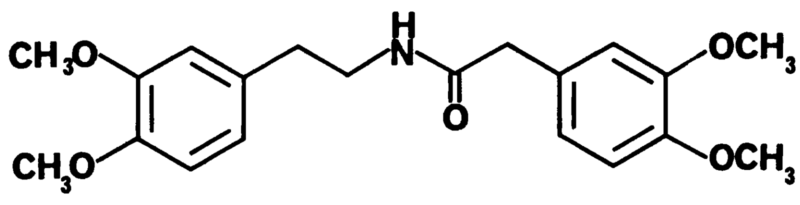
(10)

(iii) Anodic Oxidation of the Amide (10)

The anodic oxidation of this amide (10) in dry acetonitrile and sodium perchlorate under similar experimental conditions to those previously described, resulted in rapid electrode filming. Pulsing techniques, addition of potassium carbonate, or changing the electrolyte had little effect on the course of the reaction. Repeated removal and cleaning of the electrode allowed us to pass just under 1F mol^{-1} of current through the cell, but on work-up it was clear from thin layer chromatography, that only the starting amide (10) was present together with many minor unresolved components. At this point investigation of this compound was discontinued.

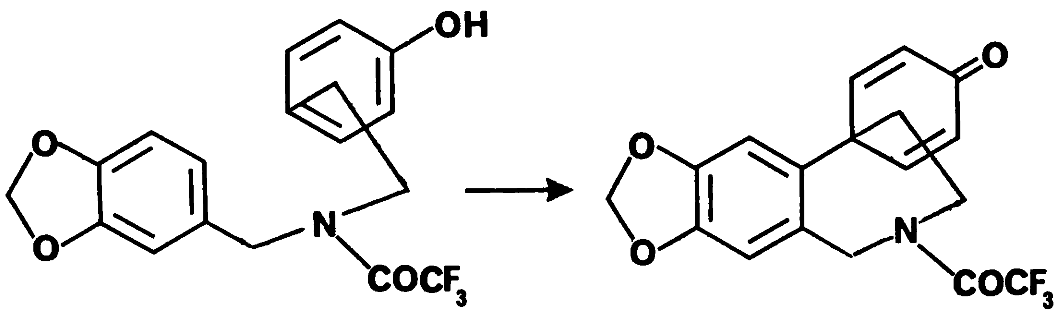
The final compound examined in this sequence was N-homoveratroyl-homoveratrylamine[12] (11) which was prepared in a similar manner to that of (10), by the combination of readily available homoveratrylamine and homoveratroyl chloride.

The anodic oxidation of the amide (11) followed a now familiar course, with severe electrode filming, irrespective of the various anodic conditions employed.



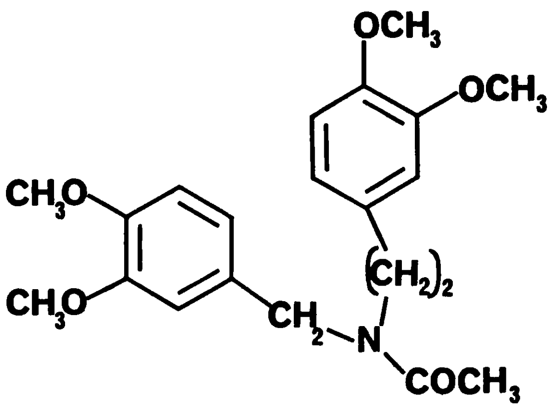
(11)

At this stage, after several unsuccessful attempts to effect intramolecular cyclization, we were eager to prove that our equipment and experimental conditions were satisfactory, and thus it was necessary to design, synthesise and electrolyse a substrate that was fairly certain to undergo intramolecular coupling. Fortunately, about this time, Kotani[13] reported the successful anodic oxidation of the phenolic amide (12) to the corresponding dienone (13).



(12) (13)

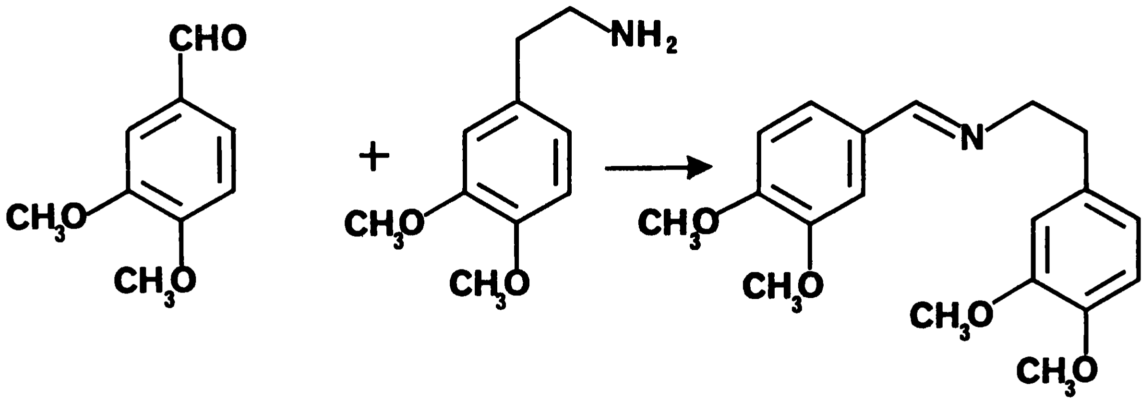
In order not to duplicate Kotani's synthesis we designed the simple analogue (14) which was prepared as follows:



(14)

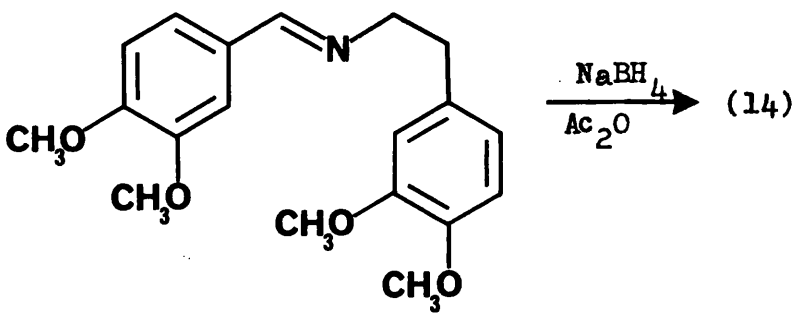
(iv) <u>The Synthesis and Oxidation of N-veratryl-N-homoveratrylacetamide (14)</u>

The condensation of homoveratrylamine with an equimolar amount of veratraldehyde gave the imine (15) in good yield, and this on reduction with sodium borohydride in ethanol



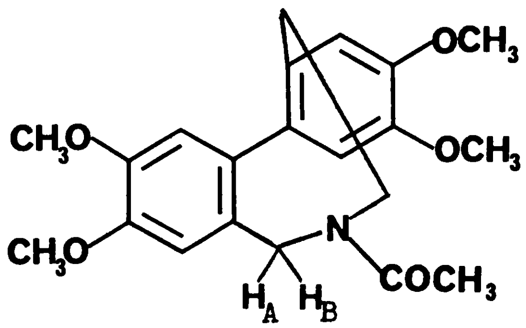
(15)

afforded veratrylhomoveratrylamine[14] (m.p. 79°). Acetylation of the amine by stirring in acetic anhydride and ethyl acetate yielded the amide (14) in an overall yield in excess of 70% from veratraldehyde.



(15)

The anodic oxidation of (14) in dry acetonitrile and sodium perchlorate under similar conditions to those previously mentioned proceeded smoothly without electrode filming at a steady anode potential of 1.15v (vsSCE). The reaction was monitored by thin layer chromatography which indicated nearly all the starting amide (14) had been consumed after the passage of 1.9F mol^{-1} of current. This analysis also showed the gradual formation of one new major component. Work-up of the anolyte afforded a dark oil which was triturated with ethanol to give a colourless powder (m.p. 190°C), which exhibited a band at $1630cm^{-1}$ in the infra-red spectrum. Mass spectral examination revealed a molecular ion peak two mass units less than that of the starting material ($M^{+\cdot}$ 371) and the ^{1}H n.m.r. spectrum showed four singlet peaks, each one due to one proton in the aromatic region. From this data it was clear that the azocine (16) had been formed.



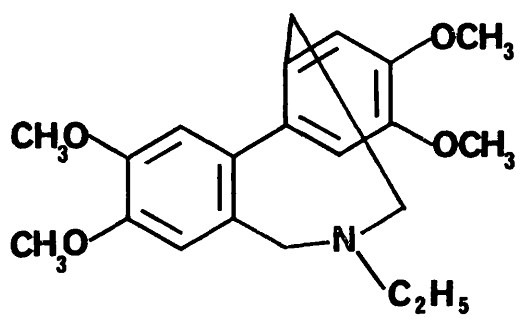
(16)

Further evidence on this point was gleaned from the ^{1}H n.m.r. spectrum; thus the two protons H_A and H_B in (16) are obviously non-equivalent and resonate at δ=5.30 and δ=3.10 with an associated coupling constant $\underline{J}$ of 14 Hz. Molecular models show that one proton lies in the deshielding zone the amide group, while the other is relatively shielded, lying perpendicular to the amide plane[15].

This was our first positive result, but despite the fact that this product contained the type of dibenzoazocine system with which we were interested, from a pharmacological point of view, the biological assay of it turned out to be negative, which prompted us to remove the N-acetyl group since it was felt that the corresponding amine might prove more active in various routine screens.

Prolonged heating of the amide (16) with either mineral acid or strong alkali failed to cleave this function, and the compound was returned unchanged. Kametani has also reported difficulty in the hydrolysis of similar amides[16] and so attempts to isolate the free base were abandoned.

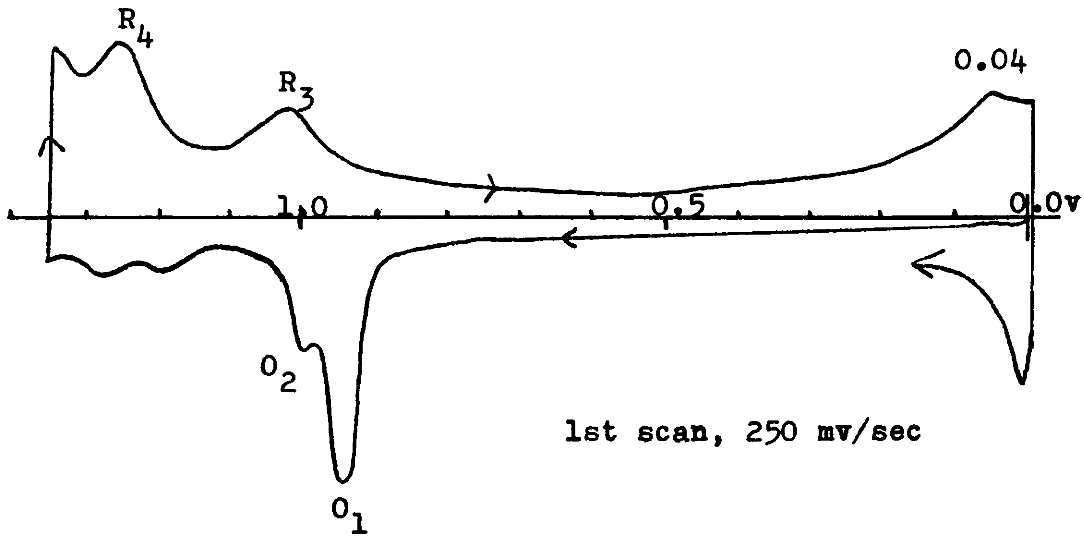
Instead lithium aluminium hydride reduction of the amide (16) in boiling tetrahydrofuran proceeded smoothly to yield the corresponding N-ethyl derivative (17), but again the pharmacology of this substance proved uninteresting in subsequent tests.



(17)

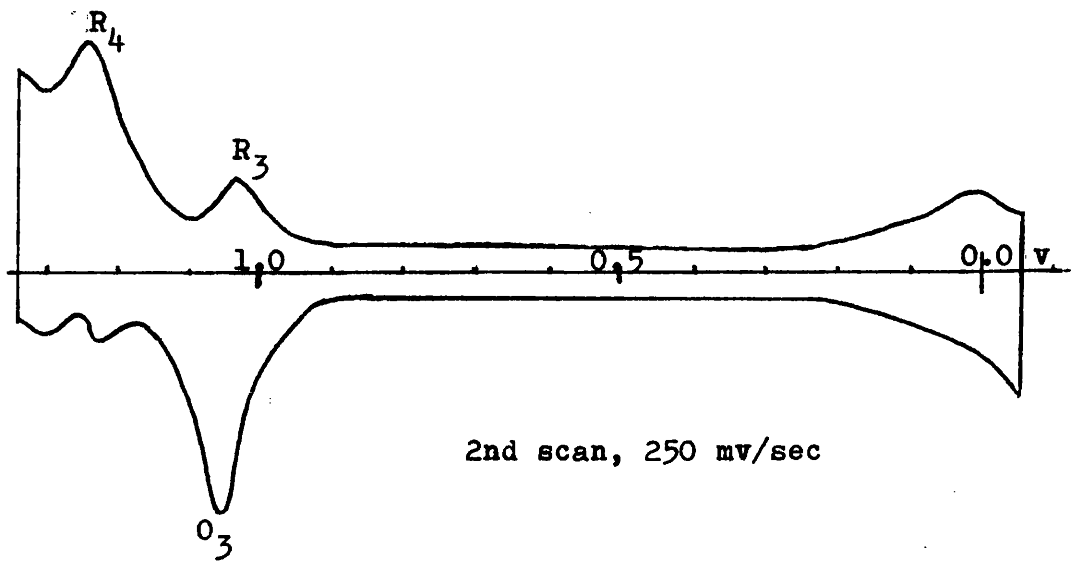
From a mechanistic view point, the cyclic voltammogram of the acetamide (14) proved quite revealing (figure 1). On the first anodic sweep (250 mv/sec) an irreversible oxidation peak occurred at 0.95v (vsSCE) (O_1) with a small shoulder peak at 1.00v (O_2), the intensity of the latter was shown to be scan rate dependent, indicating it to originate from a chemical product. Two small oxidation peaks at 1.21v and 1.29v were also present. The integrated intensity of the major oxidation peak (O_1) corresponds to a two electron process, (comparison with the first oxidation wave of an equimolar solution of 1, 4-dimethoxybenzene, the usual standard[17]).

Figure 1



On the reverse scan a broad reductive peak at 1.26v (R_4) and a smaller peak at 1.02v (R_3) were observed. The cathodic peak at 0.04v is due to the reduction of protons[17] which are generally present when a chemical reaction follows initial ionisation and is then followed itself by further oxidation. On the second and subsequent scans (figure 2) O_1 and O_2 were absent and replaced by a new oxidative peak at 1.05v (O_3), but the reductive sweep varied little from that of the first scan.

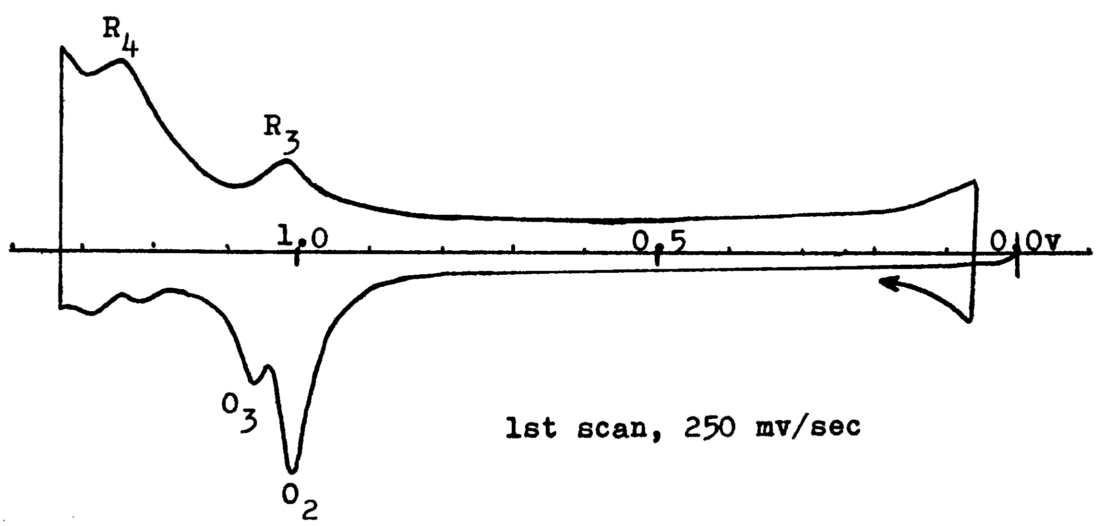
Figure 2



2nd scan, 250 mv/sec

Cyclic voltammetry of the azocine (16) at 250 mV/sec showed on the first sweep an irreversible one electron peak at 1.00v (vsSCE) (O_2) with a shoulder at 1.05v (O_3) and two further oxidative peaks at 1.21v and 1.24v (figure 3) The latter two peaks were also present in figures 1 and 2 whereas cathodic peaks at 1.26v (R_4) and 1.02v (R_3) corresponded exactly to that shown by the amide (14).

Figure 3

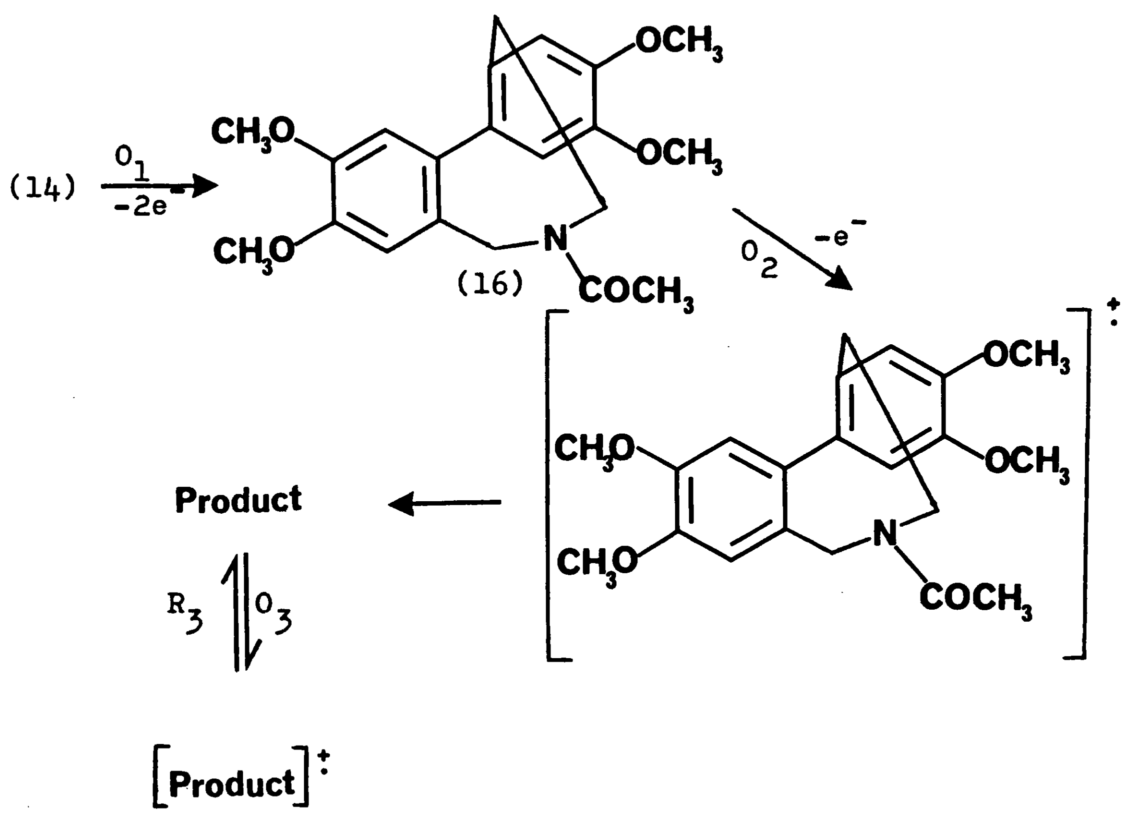


1st scan, 250 mv/sec

The second and subsequent sweeps of (16) produced a cyclic voltammogram that was almost identical to figure 2.

In summary then, this data indicates that the amide (14) undergoes a two electron oxidation to give the corresponding dication diradical which then participates in a fast chemical reaction to form the azocine (16). This product may be further oxidized at 1.00v; here however, the process is irreversible. Finally the oxidized azocine itself yields an unknown product which is reversibly oxidized at O_3-R_3. This sequence of events is illustrated in Scheme 1.

Scheme 1

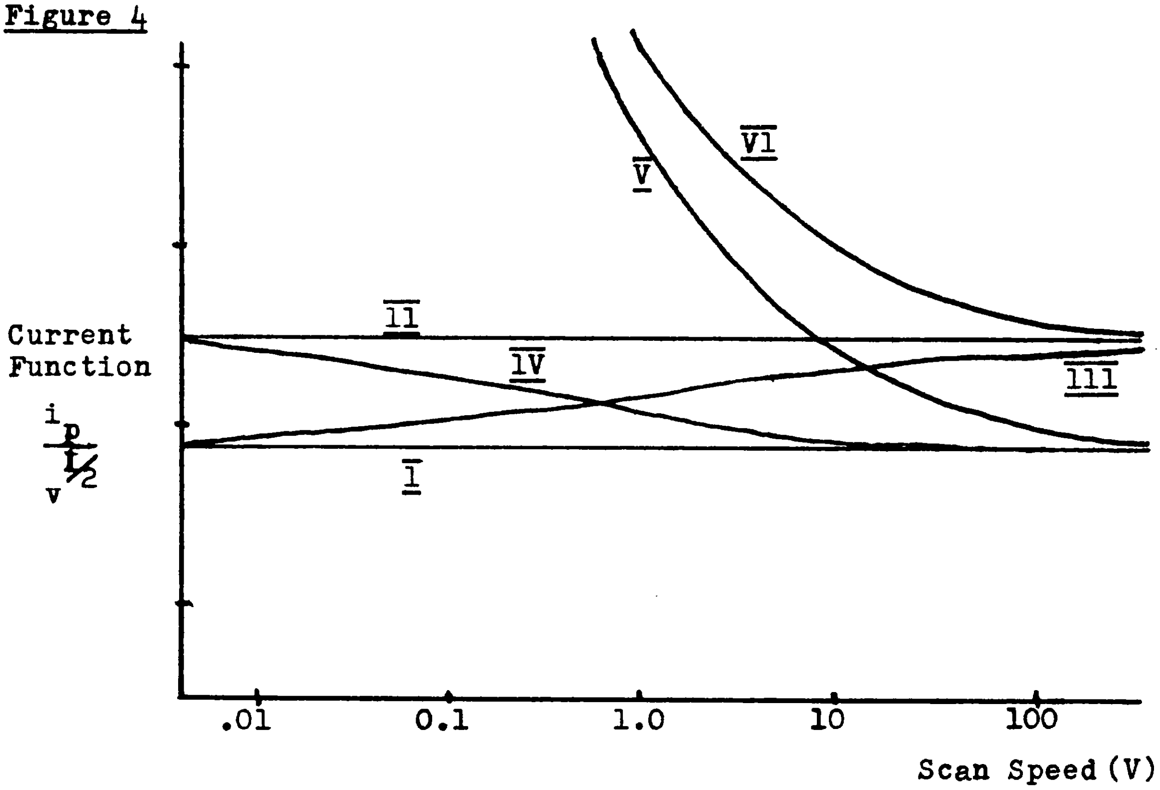


Our preparative experiment was conducted at an anode potential of +1.15v and stopped after the equivalent of 2F mol^{-1} of current had been utilized. The yield of the azocine was 66% and it is easy to see why it was not quantitative, because the anode potential used was sufficiently high to allow oxidation of the product and the formation of by-product. Unfortunately the difference between O_1 and O_2 is only 0.05v and with existing equipment precise control of the anodic potential to better than $\pm$0.05v during the whole course of the electrolysis is extremely difficult; so it is doubtful if overoxidation could be entirely prevented. An examination of the mother liquors after the isolation of the azocine failed to detect any of the anticipated by-product and this disappointing result was compounded, since an electrolysis of the purified azocine (16), at an anode potential of +1.00v and termination after the passage of 1F mol^{-1}, was also unproductive. The structure of the second compound must therefore remain a mystery.

Nicholson and Shain[18,19] have reported the solution of complex differential equations, relating the current (i) to rates of diffusion, coupled chemical reaction and the potential scan. A number of common electrode processes including coupled chemical reactions of several varieties were investigated. Special interest to the organic electrchemist lies in the fact that their results predict qualitatively the way in which a number of characteristics of the cyclic voltammogram should depend on scan rate for a given electrode mechanism. One may therefore measure these changes as a function of scan speed and deduce information concerning the electrode process.

For example, when the peak current (ip) of a wave is divided by the square root of the scan speed (current function) and this is then plotted against the scan speed (v), various characteristic curves and straight lines are obtained. Several of these plots are shown in figure 4 and type of electrode process deduced from the data enumerated in the following sequence:

<u>Figure 4</u>



Types of electrode process.

<u>Case I</u> Reversible charge transfer $R - ne^- \rightleftharpoons O$

<u>Case II</u> Irreversible charge transfer $R - ne^- \rightarrow O$

<u>Case III</u> Reversible charge transfer followed by a reversible chemical reaction $R - ne^- \rightleftharpoons O$ $O \rightleftharpoons R^1$

<u>Case lV</u> Reversible charge transfer followed by an irreversible chemical reaction $R\text{-}ne^{-} \rightleftharpoons O,\ O \longrightarrow R^{1}$

<u>Case V</u> Reversible charge transfer with a catalytic reaction $R\text{-}ne^{-} \rightleftharpoons O,\ O + Z \longrightarrow R^{1}$

<u>Case Vl</u> Irreversible charge transfer with a catalytic reaction $R\text{-}ne^{-} \longrightarrow O,\ O + Z \longrightarrow R^{1}$

Where R = neutral substance, O = oxidized species, Z = reactant, R^{1} = product.

(No effort is made to balance these equations electronically).

Taking advantage of this scheme, the variation of the peak height of O_1 for the amide (14) (10^{-3}M) was measured for various scan speeds, the results being collected in table 1 and shown graphically in figure 5. The peak currents were measured for the first cycle only and sufficient time elapsed between sweeps for initial concentration conditions near the electrode to return to normal.

<u>Table 1</u>

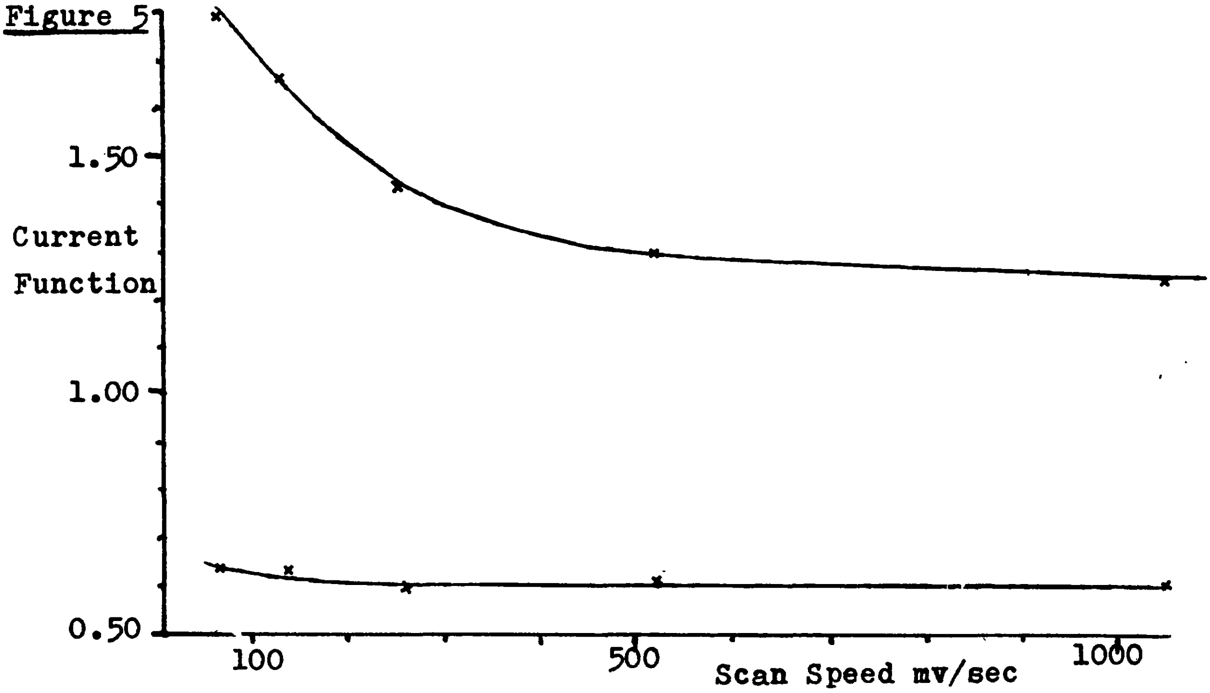
Scan Speed	Peak height (O_1)	$i_p v^{\frac{1}{2}}$	E_p volts
65 mv/sec	14.4	1.79	0.92
130 "	18.8	1.65	0.93
260 "	22.5	1.42	0.95
520 "	28.9	1.29	0.99
1040 "	40.0	1.24	1.03

The results of quantitative measurements for the first oxidative peak for 1,4-dimethoxybenzene (table 2) are included in figure 5 and thus it may be seen that at higher scan speeds (<u>ca</u>. lv/sec), the current function values for the amide (14) indicate that just over two electrons were being transferred.

Table 2

Scan Speed	Peak height	$i_p/v^{1/2}$
65 mv/sec	5.1	0.64
130 "	7.1	0.63
260 "	9.6	0.60
520 "	14.1	0.62
1040 "	19.3	0.60

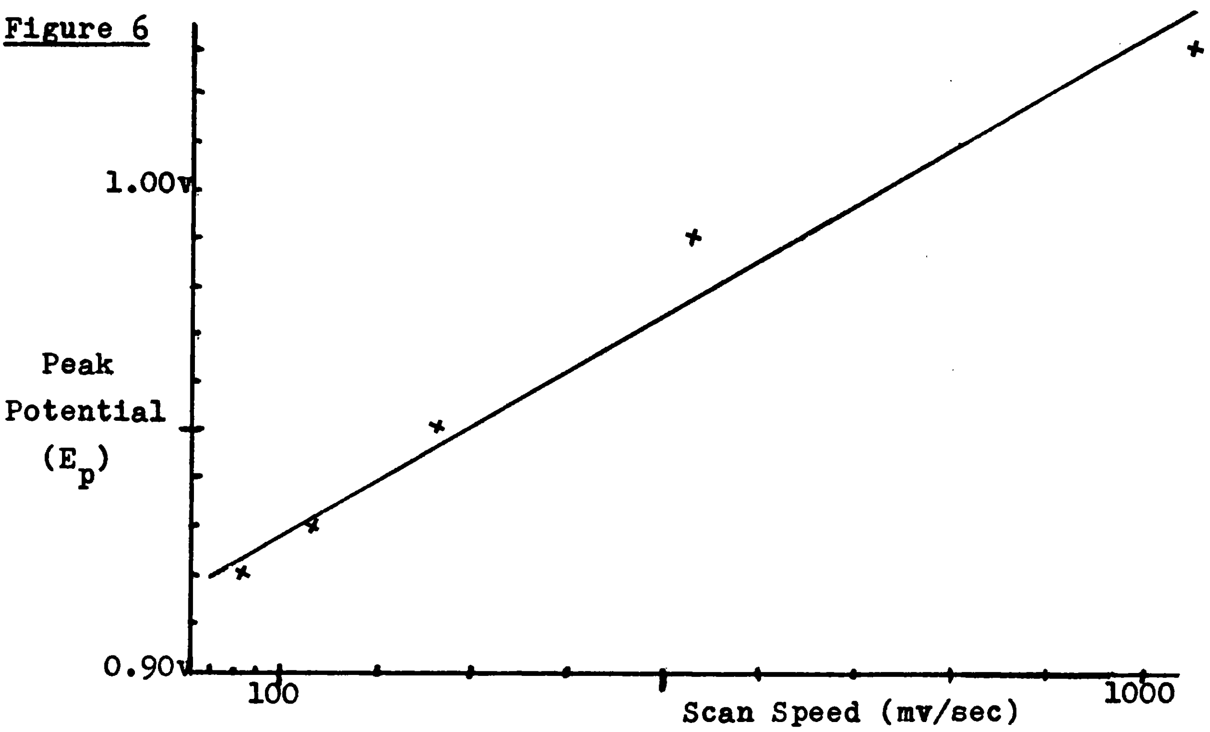
Figure 5



At slower scan speeds nearly three electrons were being transferred and we assume that further oxidation of the chemical product (16) occurs in this range. Further evidence that a chemical reaction occurs at, or very close to, the first oxidative wave (O_1) can be seen from the fact that the peak potential values (E_p, table 1) are linearly related to the scan speed[20] as shown in figure 6.

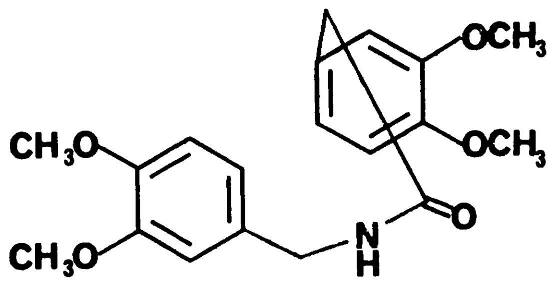
The fact that oxidation of the chemical product (16) can be outrun by increasing the scan speed to 1v/sec implies

Figure 6

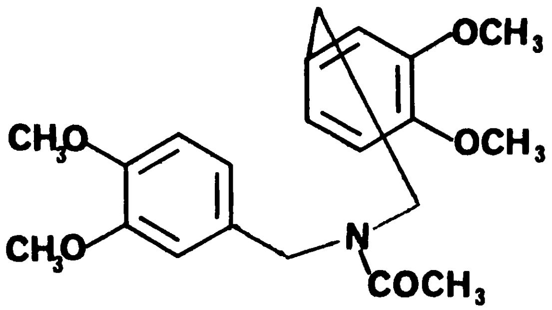


that the coupling of the two aryl nuclei is slow. The other possible rate determining step in the formation of the azocine (16) is the loss of two protons from the coupled intermediate, but this is normally an extremely rapid process as shown by Parker in the anodic oxidation of bibenzyl's to the corresponding phenanthrenes[21]. In the latter case, cyclic voltammetry showed a single four electron peak, which was attributable to a two electron oxidation of the bibenzyl to give the dihydrophenanthrene which was simultaneously oxidized to the fully aromatic system. Attempts to differentiate the two electrode processes by the use of high scan speeds and rotating disc electrodes failed[21];thus it is apparent that the length and nature of the link adjoining the two aryl nuclei affects the kinetics of cyclization.

The reason for our original interest in the electrochemical oxidation of the tertiary amide (14) was firstly to establish the most suitable experimental conditions, and secondly to compare the results with those previously obtained for the secondary amide (6).

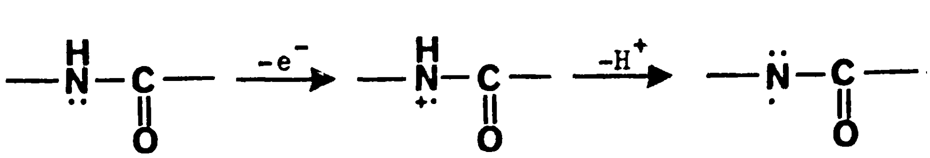


(6)



(14)

Both compounds on coupling should give an eight membered ring and both have the same aromatic substitution pattern. The only obvious difference between the two structures is the nature of the amide moiety; thus, since the other secondary amides (10) and (11) also failed to cyclize we were given to the opinion that this function was not electrochemically inert. We postulated that direct oxidation of the nitrogen atom in a secondary amide might be followed by the facile loss of a proton to establish a stable radical, which could then polymerize and cause the observed electrode filming.

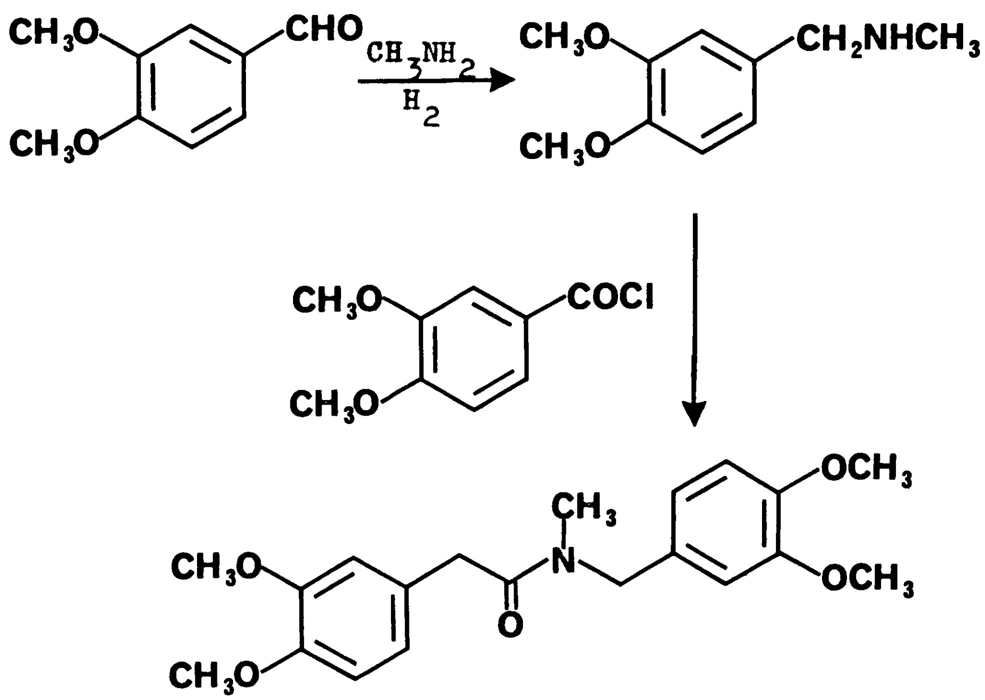


A tertiary amide could not deprotonate in this way and thus its intramolecular cyclisation would not be impeded.

The simplest way of checking this postulate was to replace the -NH group in compound (6) by an N-Me function and repeat the experiment.

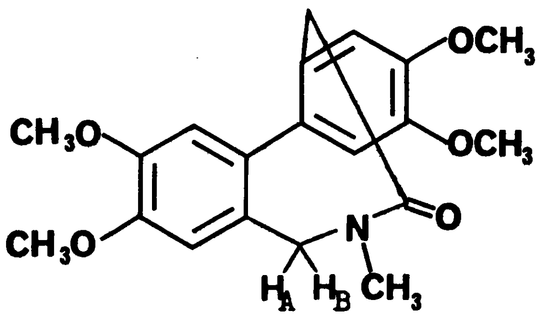
(v) <u>Preparation and anodic oxidation of N-methyl-N-veratryl-3, 4-dimethoxyphenylacetamide (18)</u>

As the secondary amide (6) was readily available, we anticipated metalation of the nitrogen followed by reaction with methyl iodide would offer a simple route to the tertiary amide (18). However, repeated attempts to effect the first step with sodium amide in dry benzene[22] failed, but the amide may be prepared simply by the reaction of N-methylveratrylamine and homoveratroyl chloride in the presence of base. Reductive amination of methylamine and veratraldehyde proved an effective way of synthesising N-methylveratrylamine.



(18)

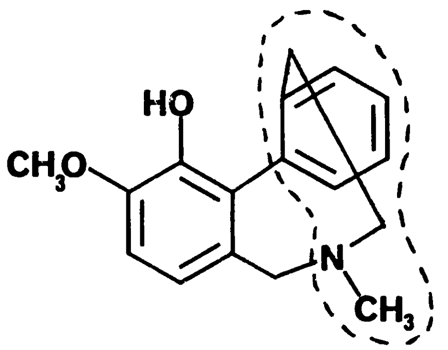
The electrolysis of (18) in acetonitrile proceded smoothly at 1.15v (vsSCE) until nearly 2F mol^{-1} of current had been consumed. Continuous T.L.C. analysis during the course of the reaction showed the gradual disappearance of the starting substrate, with the simultaneous formation of one new component, and work-up of the anolyte gave a brown viscous oil, which upon trituration with ethanol afforded a colourless powder (m.p. 204-205°C). Mass spectroscopic examination showed a molecular ion two mass units lower (m/e 357 M^+) than that of the starting material and the ^1H nmr spectrum exhibited four singlet protons in the aromatic region (δ 6.90-6.95). The infra-red spectrum contained a typical amide carbonyl band at 1640 cm^{-1}, and from this physical data, it was clear that the coupled product (19) had been formed.



(19)

Additionally the ^1H nmr showed a geminal interaction between the two protons H_A and H_B which resonate at $\delta = 3.10$ and 3.57 (J = 14Hz), this situation being similar to that previously noted for the azocine (16).

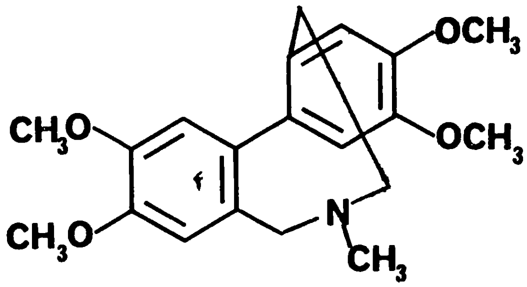
The smooth electrolysis of the tertiary amides (14) and (18) not only tended to confirm our suspicions that secondary amides are poor substrates for anodic oxidation, but provided us with a product, the molecular skeleton of which is not unlike that of the drug Apotamine[23] (20) which is used in some countries for treating cardiovascular diseases.



(20)

Although the aromatic substitution pattern of the azocine (19) is somewhat different, reduction with lithium aluminium hydride would provide an interesting analogue of Apotamine, containing the familiar β-phenylethylamine fragment (dotted line), a common feature of many drugs which act on the central nervous system[24].

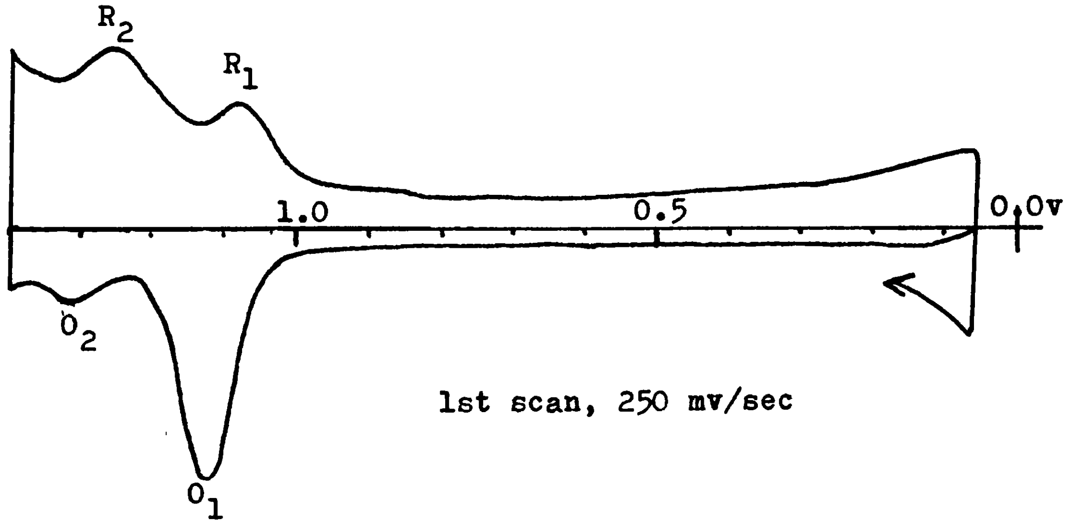
Lithium aluminium hydride reduction of the amide (19) in boiling tetrahydrofuran (T.H.F.) during four hours gave a good yield of the tertiary amine (21) (m.p. 136-137°C) and it was gratifying to note that the infra-red spectrum of this tertiary amine (21) was almost identical to that of the N-ethyl homologue (17), the two compounds being prepared by two different routes. Unfortunately these compounds show only marginal activity in various pharmacological tests and thus are of little value.



(21)

Cyclic voltammetry at 250 mV/sec of the tertiary amide (18) using a platinum bead electrode showed on the first sweep, a broad oxidative wave with a peak potential (Ep) of 1.11v (<u>vs</u> SCE). Quantitative measurements were difficult because of the shape of this peak, but the overall intensity corresponded to the removal of more than two electrons (figure 7).

<u>Figure 7.</u>



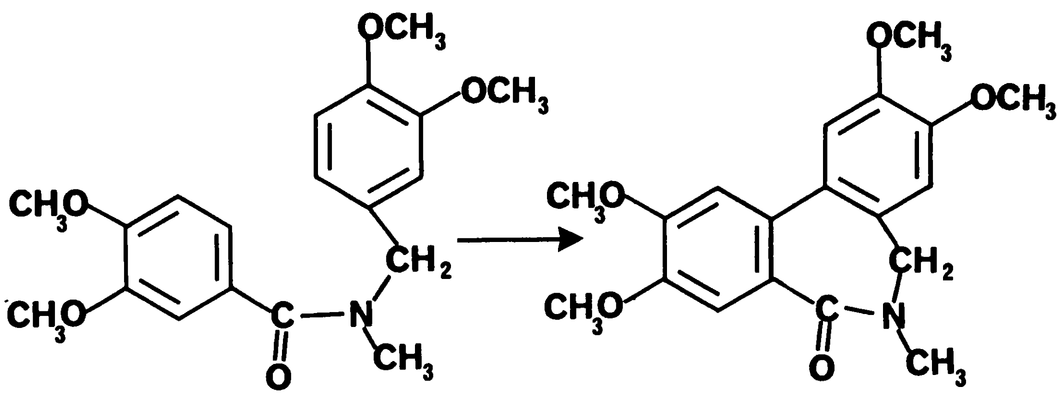
1st scan, 250 mv/sec

A smaller anodic peak at 1.32v (O_2) was also present on the first scan and formed a redox couple with a cathodic maximum at 1.26v (R_2). A broad poorly defined cathodic peak was present at 1.09v (R_1), possibly associated with O_1.

Cyclic voltammetry of the cyclized product (19) showed that it underwent oxidation at 1.05v, a process which was reversible at higher scan speeds (<u>ca</u>. 800 mV/sec). Oxidation at this potential gave rise to a chemical product which formed the redox couple (O_2-R_2) shown in figure 7. Thus the broad nature of the oxidative peak (O_1) for the amide (18) is no doubt caused by oxidation of the product (19) which is rapidly formed; and hence explains why peak (O_1) measured more than two electrons. This could also be a factor in explaining the lower yield of cyclized product (19) (45%), compared to the yield of (16) which is 66%, the former being overoxidized in the preparative experiment. The nature of the species which gives rise to the couple (O_2-R_2) is uncertain.

(vi) <u>The Synthesis of azepines</u>:- success in the synthesis of (19) led us to examine the anodic oxidation of similar compounds leading to seven membered lactam structures, as considerable interest was expressed by Allen and Hanburys in this type of compound[25], and in order to progress in this direction N-methyl-N-veratryl-veratramide (22) was prepared, by the reaction of veratroyl chloride and N-methyl-veratrylamine. Anodic oxidation of the amide (22) in acetonitrile at an electrode potential of 1.15v (<u>vs</u>SCE) proceeded with the formation of a dark brown anolyte until

1.5 F mol^{-1} of current had been passed. At this point, T.L.C. analysis showed very little starting material to be present, but an almost continuous unresolved streak and only one minor fast running component was indicated. Column chromatography (SiO_2 Ethylacetate/Pet. ether) afforded a small amount of colourless powder (m.p. 220-222°C), which had two mass units less than the starting material (m/e, 343, M^+). The ^1H nmr spectrum clearly shows four singlet proton resonances with little change in the rest of the spectrum compared with the starting amide. No other products were isolated in a sufficiently pure state for spectral analysis. We judged the product to be the desired tricyclic compound (23), but the extremely poor yield (~2%) was disappointing, especially as in order to obtain enough for screening purposes the whole tedious operation would have to be repeated several times. In the event this was not done, mainly due to the pressure of other work.

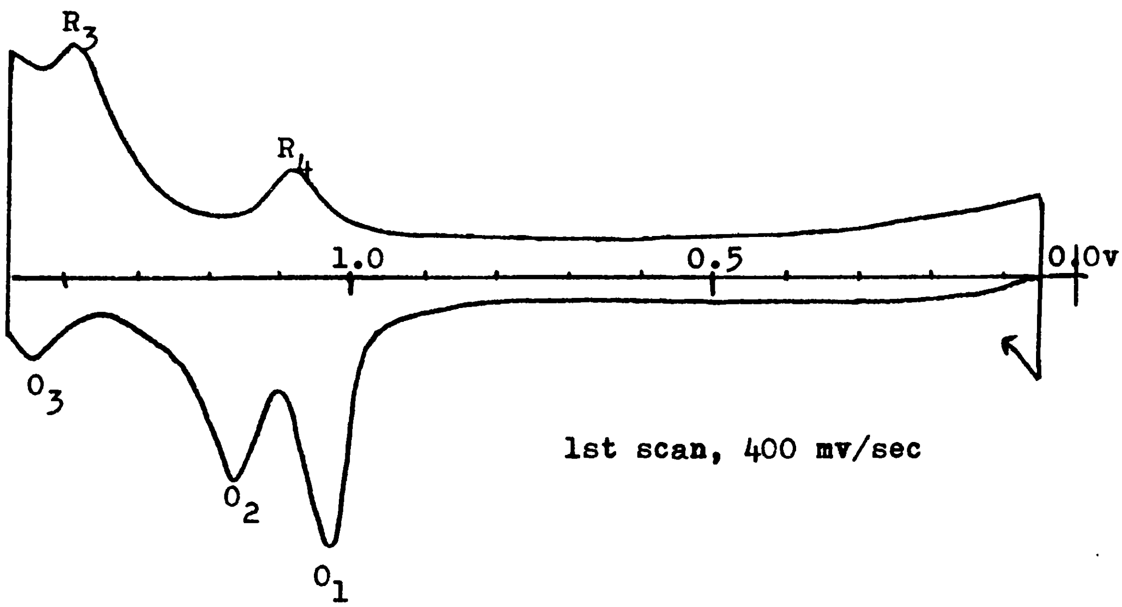


(22) (23)

Cyclic voltammetry of the starting material (figure 8) however, gave a good insight into the reasons for the poor productivity of this reaction.

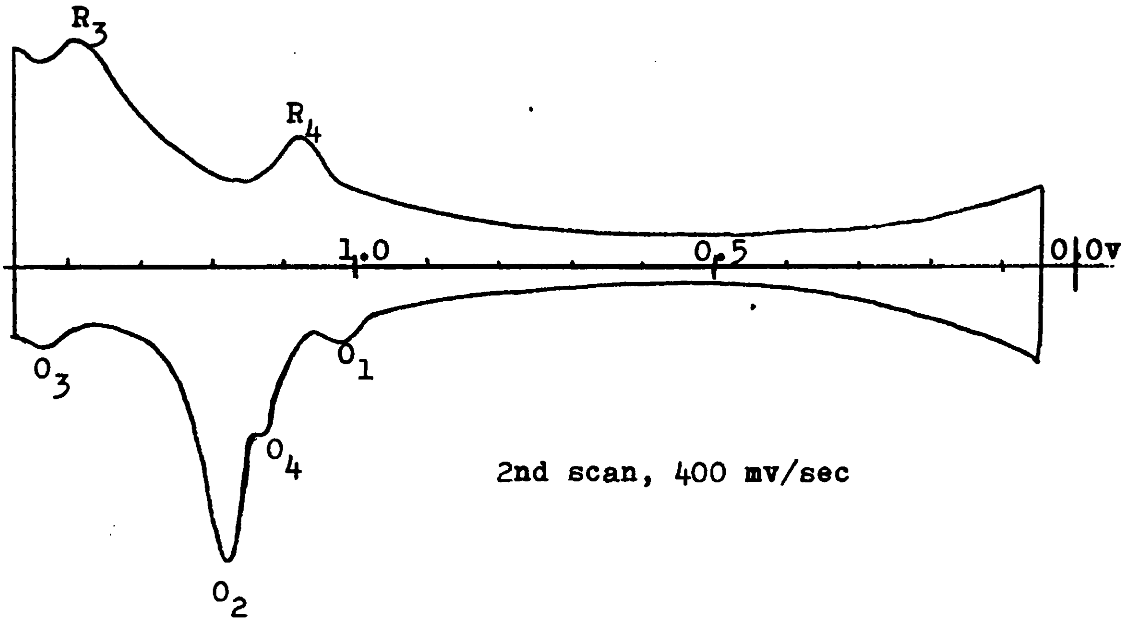
On the first anodic sweep initial electron abstraction occurs at 1.02v (O_1), this is followed by a second oxidation process at 1.18v and a third anodic reaction at 1.43v (O_3). This last oxidative wave forms part of a redox couple, the associated reduction peak being at 1.39v (R_3). Finally there is a reduction peak at 1.00v midway between O_1 and O_2 (since at this point its identity cannot be judged with certainty, it is assigned R_4).

Figure 8



On the second scan (Fig. 9) O_1 almost disappears while O_2 and R_4 remain almost unchanged. A new anodic peak O_4 is now apparent at 1.13v and this appears to form a couple with R_4. Repeated scanning causes diminution of all peaks except O_3-R_3.

Figure 9



The two consecutive electron transfers, O_1 and O_2, were shown to be due to the removal of one electron from the 3, 4-dimethoxy-benzyl and -benzoyl units respectively. (A sample of N-benzylveratramide showed a reversible couple at 1.20v (vs SCE). The reason for this difference in oxidation potentials (0.16v) can easily be attributed to the deactivating influence of the amide carbonyl group on the adjacent aryl nucleus.

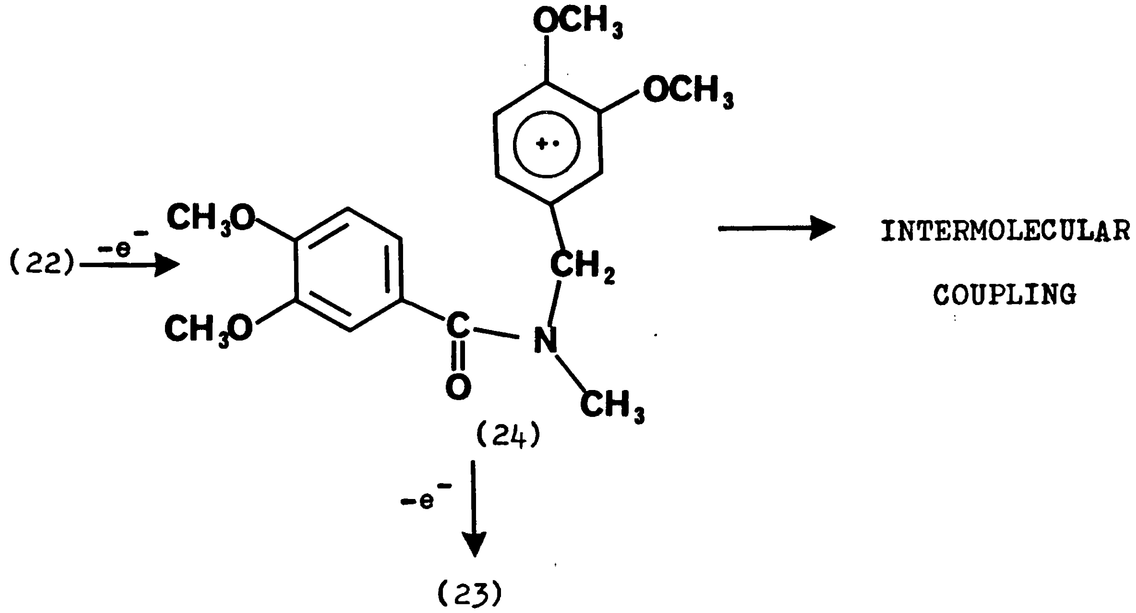
Interestingly, if the scan was stopped at potentials below O_2, the first anodic peak O_1, becomes completely reversible, thus implying that product formation occurs via a dication diradical which is only produced at potentials greater than O_2. Such a view contradicts Nyberg's hypothesis concerning the mechanism of coupling of aryl rings[26].

Cyclic voltammetry of the cyclized product (23) showed the first electron transfer at a position corresponding to O_4 (Fig. 9) and repeated scanning gave a cyclic voltammogram very similar to that of the starting amide after several sweeps. Further evidence that the dication diradical is necessary for coupling was gleaned from the application of potential step cyclic voltammetry (P.S.C.V.)[27], which involves two steps. The first stage requires the stepping of the electrode potential to the region of interest followed by return to zero volts and a rapid scan to observe the follow-up products.

Application of P.S.C.V. to the amide (22) necessitated holding the electrode potential at O_1 for ten seconds, followed by immediate return to zero volts and a scan. The result was a cyclic voltammogram very similar to that of Fig. 8, which indicated that the azopine (23) was not being formed at the potential of the first oxidative peak.

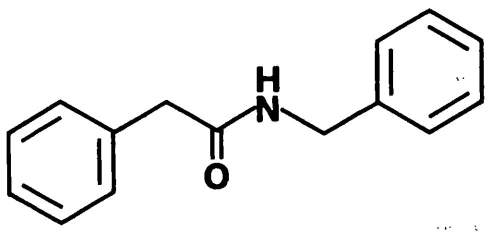
As the preparative oxidation was carried out at 1.15v (vsSCE) it is unlikely that much of the dication species was formed[28], since a potential close to 1.20v is required for its production. More probably the mono cationic species (24) (scheme 2) formed at the lower potential, enters into intermolecular coupling processes and this factor would then account for the observation that most of the starting material disappeared after just 1.5 F mol^{-1} of current had been passed. Unfortunately this cyclic voltammetric evidence was not available until some time after the experiment had been conducted and time did not

Scheme 2

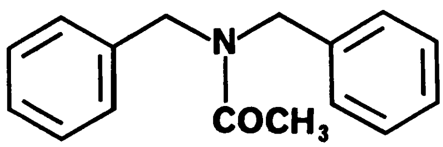


permit the re-examination of the anodic oxidation of the amide (22) at higher current densities. Conditions which would have served to force the anode potential to a value favouring intramolecular coupling.

The absence of electrode filming in the anodic oxidation of (22) further strengthened our belief that the secondary amide function was electroactive and as soon as we had constructed our own cyclic voltammetric instrument, midway through the project, we set out the investigation of the problem and to begin with, we selected N-benzyl phenylacetamide (25a) as a model.



(25a)



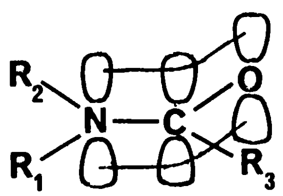
(25b)

This compound is, of course, analogous to our earlier electrochemical substrate (6), but lacks the methoxy groups in the two aryl rings. If our view were to be correct, then there should be an oxidation peak in the cyclic voltammogram of this compound at a relatively low potential, due to the ionization of the lone pair of electrons on the nitrogen atom. In the event, however, an anodic scan of the secondary amide revealed no such peak below +1.80v and thus our argument was demolished.

Similar results were obtained with N,N-dibenzyl acetamide, (25b), and this led us to consider what other factors could operate.

The reason for amide stability towards electrophiles compared with amines is explained by delocalization of the lone pair of electrons on the nitrogen atom with the adjacent carbonyl function, thereby inducing an electron defficiency on the nitrogen. For most effective delocalization, the nitrogen atom must become sp^2 hybridised and the p-orbitals must be aligned with the p-orbitals on the adjacent carbon atom (Fig. 10), thus causing the amide to take up a planar configuration.

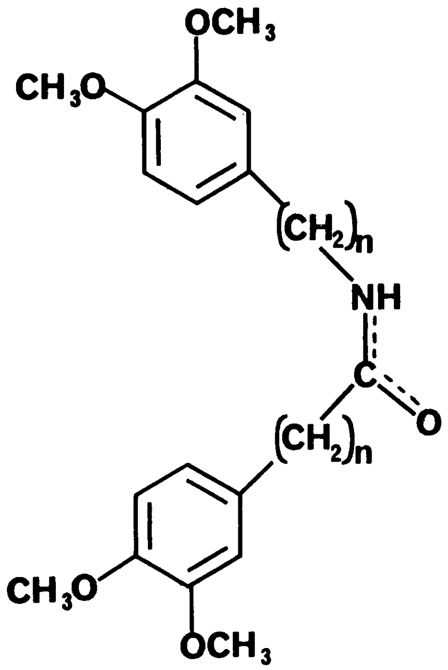
Figure 10



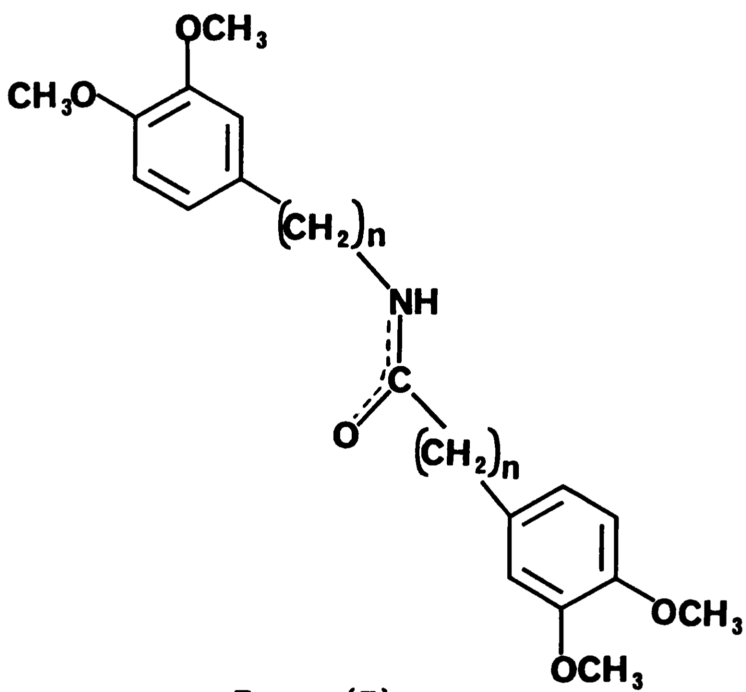
This conjugation obviously increases the carbon to nitrogen bond order with a simultaneous reduction in the carbon to oxygen double bond character. The latter can be gauged by the stretching frequency of the carbonyl absorption in the infra-red spectrum, thus dibenzyl amides typically exhibit this band at 1640 cm^{-1} indicating considerable polarity.

The presence of partial double bond character in the C-N bond will restrict rotation and hence this may have stereochemical implications as far as our substrates are concerned. Clearly if the barrier to rotation is sufficiently high at room-temperature and the amide happens to exist in an unfavourable 'conformation' (figure 11), intramolecular aryl-aryl coupling could not occur. The situation in fact would not be unlike that of the photochemical coupling of <u>cis</u>- and <u>trans</u>- stilbenes.

<u>Figure 11</u>



<u>Cis</u> (Z)

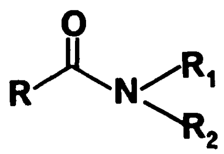


<u>Trans</u> (E)

A literature search showed a considerable volume of work had been published on restricted rotation of amides, culminating in a comprehensive review by Stewart and Siddall[15].

For the general amide with structure $\underline{x}$ (figure 12) where the groups $\underline{R}_1$ and $\underline{R}_2$ are nominally the same, each prove to be both magnetically and geometrically non-equivalent. Also, the amide forms an approximately planar framework with a large barrier to interconversion. The

Figure 12



occurrence of separate signals for groups $\underline{R}_1$ and $\underline{R}_2$ has been attributed to the anisotropy of the carbonyl group[29]. It is suggested that shielding conical regions exist above and below the amide plane while a large deshielding zone is present in the plane. Separate signals will only be observed when rotation around the C-N band is slower compared with the timescale of the nmr measurement.

i.e., $T_A \qquad \dfrac{2}{2\ (V_A - V_B)}$

where T_A = mean lifetime at site A

V_A and V_B are resonant frequencies at sites A and B.

Therefore, if it is possible to assign separate cis and trans signals it is not difficult to calculate the ratio of the two isomers, however, the absence of separate peaks does not necessarily imply only one conformer is present or that rapid rotation is occurring as other factors cause chemical shift degeneracy.

Although no data relating to amides analogous to (6) could be found, Table III indicates the established isomer ratio of some simple secondary alkyl amides (ref. 15 p.524).

Table III

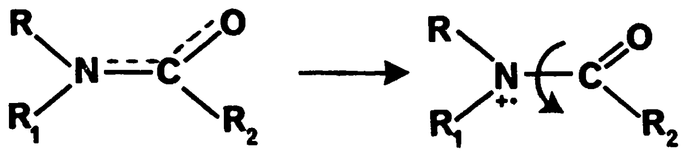
Amides of structure $RCONHR_1$

R	R_1	% trans isomer present 'E'
H	Methyl	92%
H	Ethyl	88%
Methyl	Methyl	100%
Methyl	Ethyl	100%
Ethyl	Ethyl	100%
Iso-butyl	2-propyl	100%

From Table III it is apparent that when both groups are alkyl, only the trans form exists. This predominance is attributed to simple steric considerations, the two largest groups prefering to be furthest apart in space.

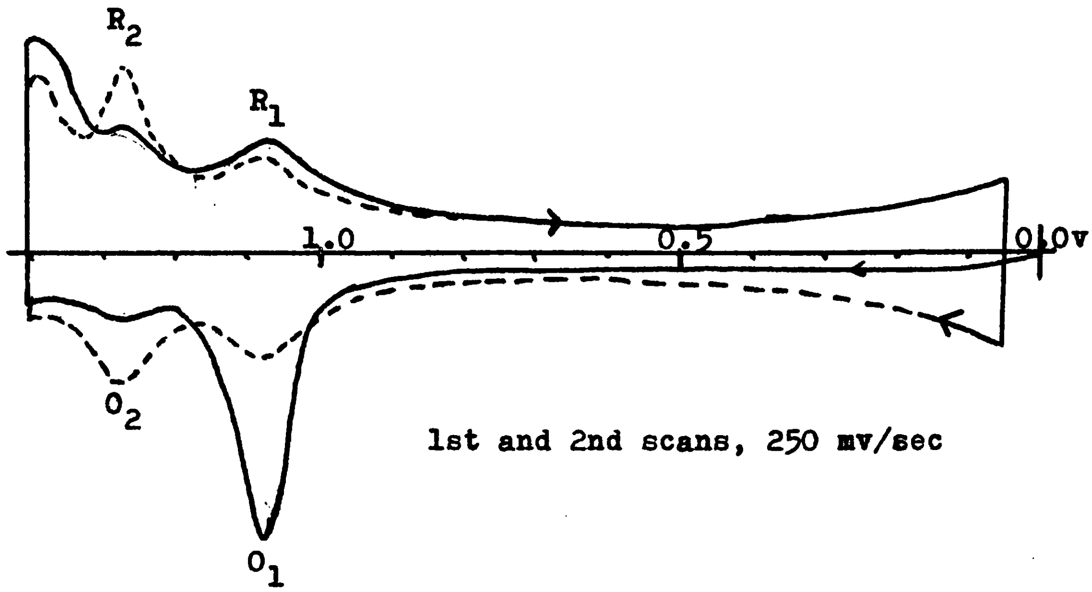
Examination of the ^1H nmr spectrum of the secondary amide (6) showed the methylene protons adjacent to the nitrogen as a doublet with peaks at $\delta = 4.24$ and $\delta = 4.30$ which was at first surprising, as from Table III it would be expected that the amide would exist predominantly in the trans (E) form. The presence of two peaks, however, was due to coupling from the N-H as proved by deuteration; temperature having little effect on the peak separation (J = 6Hz).

Attempted nuclear Overhauser enhancement experiments[30] on the amide (6) failed to show any increased integral ratios when either of the methylene resonances or the N-H resonance were irradiated, and so direct evidence for the trans isomer could not be obtained, nevertheless, we are certain that the molecule assumes the adverse (from our viewpoint), geometry. We were, of course, aware of the geometric constraint but had believed earlier that if the amide unit itself were oxidized then the barrier to rotation would be much reduced. Now we know the amide unit is not involved and so the spatial arrangement is of paramount importance.



The stereochemistry of amide (6) also affects the cyclic voltammogram, which on the first cycle at 250 mV/sec shows a two electron anodic peak at 1.09v (vsSCE) with a corresponding broad cathodic peak at 1.08v (figure 12a). The small anodic and cathodic chemical product peaks at 1.27v (O_2) and 1.22v (R_2) increased in intensity on repeated scanning indicating they were the result of further oxidation of the chemical products, the latter in this case are probably dimeric and polymeric species which would have a similar oxidation potential to the starting

Figure 12a



material, these products giving rise to the reduced intensity peak O_1, on subsequent scanning. In general terms, we noted the cyclic voltammograms of secondary arylalkyl amides to be more poorly resolved than their tertiary amide counterparts, no doubt due to the multiplicity of possible coupling processes.

With N, N-disubstituted amides the isomer ratios are not generally so large, but usually the larger groups again prefer the trans-conformation. Table IV shows some isomer ratios of various N-methylamides indicating that quite bulky groups have little effect on this ratio.

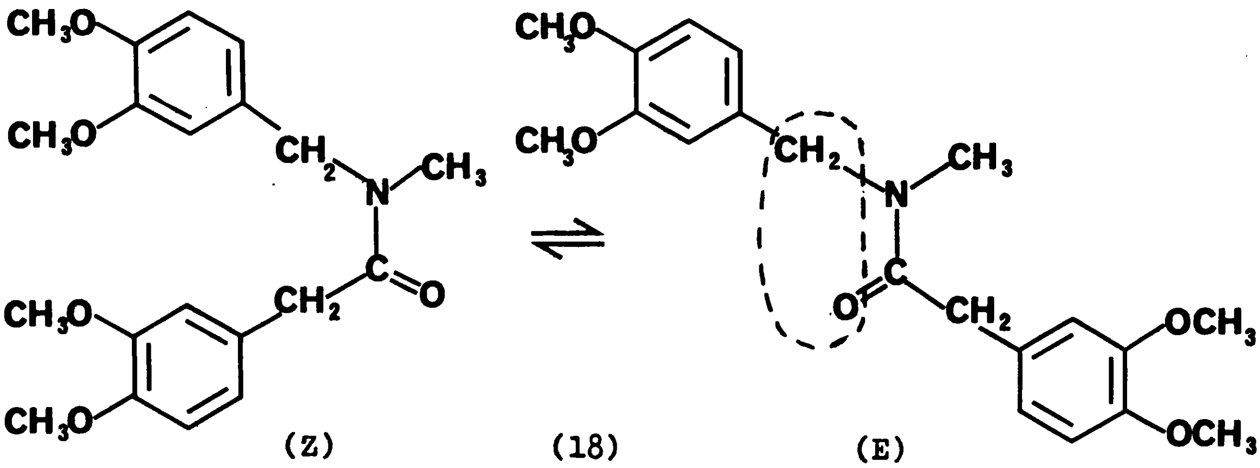
Clearly the presence of nearly equal amounts of both cis and trans forms does not imply the barrier to rotation is any less, simply that the energy difference between the two isomers is not so great as in the case of the secondary amides.

Table IV

$RCONR_1R_2$

R	R_1	R_2	% isomer with R_1 *trans* to R
Me	Et	Me	51%
Me	n-butyl	Me	53%
Me	Cyclohexyl	Me	55%
Me	2-propyl	Me	58%

Turning now to the tertiary amides, it follows that if interconversion between the isomerides is energetically unfavourable then only the Z-form can lead to the cyclized product. In the event, the yield obtained may not exceed the proportion of this isomer in the solvent system employed, (assuming rotation of the C–N band does not occurr in the mean lifetime of the *trans* cation radical). The ^1H nmr of the tertiary amide (18) at 28°C in ^3D-acetonitrile unexpectedly failed to differentiate between the chemical



(Z) (18) (E)

shift positions of the methyl resonances of the two isomerides ($\delta = 2.89$), although the methylene protons adjacent to the nitrogen atom are not degenerate and gave rise to singlet peaks at $\delta = 4.57$ and $\delta = 4.51$ in an integral ratio of 2:1 respectively. On heating to the maximum temperature possible in the solvent, 70°C, no sign of coalescence of these signals was noted. In ^{6}D-dimethylsulphoxide, however, the ^{1}H nmr spectrum of the isomer mixture was rather different and now showed two N-methyl resonances at δ= 2.89 and δ= 2.74 (integral ratio 2:1), as well as distinct singlets at δ= 4.50 (ratio 2:1) which corresponds to the $-CH_2N$-Me methylene functions.

The spectrum was run at several temperatures (see Table V) and from this it was noted that coalescence of the methyl resonances was reached at 65°C, this also applied to the methylene signals.

<u>Table V</u>

Temperature	N-methyl peak separation	$N-CH_2$-Ph separation
31°C	14 Hz	8
50°C	12 Hz	6
55°C	11 Hz	4
60°C	7 Hz	0
65°C	0 Hz	0

By the use of eq$^{\underline{n}}$ 1[31] it is possible to calculate the potential energy barrier (Ea) to overcome this restricted rotation. The graph (see p.238) was used to extrapolate the chemical shift difference of the two N-methyl resonances at 273°K. (14.9 Hz).

<u>Eq$^{\underline{n}}$ 1</u> $$Ea = 4.59, Tc \left[9.97 + \log_{10} \frac{Tc}{\delta} \right]$$

where Tc = coalescence temperature °K

δ = peak separation in Hz

Thus for amide (18), $T_c = 338^{o}K.$, $\delta = 14.9$ Hz

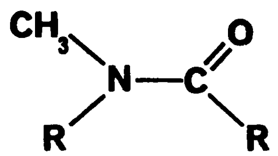
Therefore $Ea = 4.59 \times 338 \left[9.97 + \log_{10} \frac{338}{14.9} \right] \times 4.18$ Joules/mol

$Ea = \underline{\underline{78.5}}$ K Joules/mol

This value is in agreement with many other published results[15] and is certainly sufficiently high to impede rapid rotation during electrolysis.

From the ^{1}H nmr spectrum of the amide (18) in ^{6}D-dimethylsulphoxide it is tempting to ascribe the low field N-methyl resonance at $\delta = 2.89$ (major isomer) to the form with this group cis to the carbonyl group.

Figure 13

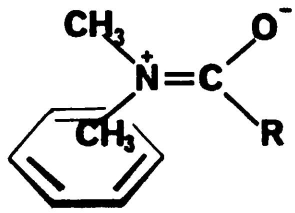


R = 3,4-Dimethoxybenzyl

The deshielding zone of the carbonyl thus affecting a downfield shift, but from steric considerations one might expect the E-isomer to predominate.

The effect of solvent on the ^{1}H nmr spectrum of the isomer mixture is interesting and recalls the suggestion by Morishima[32], that the solvent influences the degree of coupling across the C-N bond. A differential solvent effect was also noted by Hatton and Richards[33,34], in their study of the spectrum of N, N-dimethyl amides. In this case, although both resonances were shifted upfield in benzene relative to their positions in non aromatic solvents, one methyl group was influenced much more than the other. This is, of course, a familiar phenomenon and reflects the shielding interaction of the electron system of benzene in a semi structured solvent solute array. In this case the partially negatively charged oxygen atom of the amide tends to lie as far away from the π-cloud as possible, whereas the positively charged nitrogen atom remains in close contact (figure 14).

Figure 14



The methyl signal _trans_ to the carbonyl group is then shifted to a relatively high field position compared with that of the _cis_ methyl.

These findings prompted us to run the ^{1}H nmr spectrum of amide (18) in ^{6}D-benzene to see if we could observe a similar effect (see p. 225). The spectrum showed the N-methyl resonances as two well defined singlets at $\delta = 2.81$ and $\delta = 2.50$ in a ratio of 1:2 respectively, with the methylene protons adjacent to the nitrogen as two singlets at $\delta = 4.60$ and $\delta = 4.52$ in a ratio of 1:2. Examination of the two spectra, one in dimethylsulphoxide and the other in benzene solution shows that the N-methyl resonance position of the major isomer is shifted upfield by 0.39 Hz in the latter, whereas the signal of the minor component is actually deshielded (0.24 Hz). These facts tend to support the 'common sense' view that the major isomer is really the E - form i.e., the one with the largest group trans to one another; and it is clear that conclusions of amide geometry based upon nmr studies in dimethylsulphoxide solution alone may be unreliable.

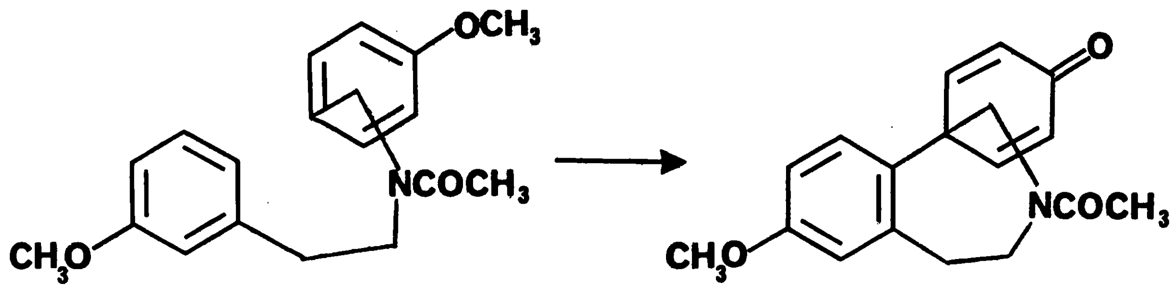
These findings are very informative because we consider the concentration of Z - isomer in solution is no greater than 33%, but the isolated yield of intramolecular coupled product (19) is 45%, which implies that some rotation about the C-N bond of the E - isomer occurs before intermolecular coupling can take place. This allows us to present scheme 3, which is a more comprehensive representation of the various electrode reactions.

Scheme 3

$$\begin{array}{lll} \underline{Z}\text{ - isomer } (33\%) \xrightleftharpoons{-2e^-} (Z)^{\ddagger}: & \xrightarrow{\text{FAST[35]}} & \text{Azocine (19)} \\ \qquad\qquad\qquad\qquad\quad \Updownarrow \text{SLOW} & & \\ \underline{E}\text{ - isomer } (66\%) \xrightleftharpoons{-2e^-} (E)^{\ddagger}: & \xrightarrow{\text{SLOW}} & \text{Intermolecular Products} \end{array}$$

Preparation and anodic oxidation of N-(p-anisyl)-N-(m-homoanisyl)-acetamide (26)

From our previous work, it seemed fruitless to carry out anodic oxidations on secondary amides, but tertiary amides are another matter. In previous cases, however, para-para coupling had always been observed and thus the selection of the amide (26) as a substrate for oxidation was considered interesting, since here, intramolecular coupling should lead to the spiro compound (27).



(26) (27)

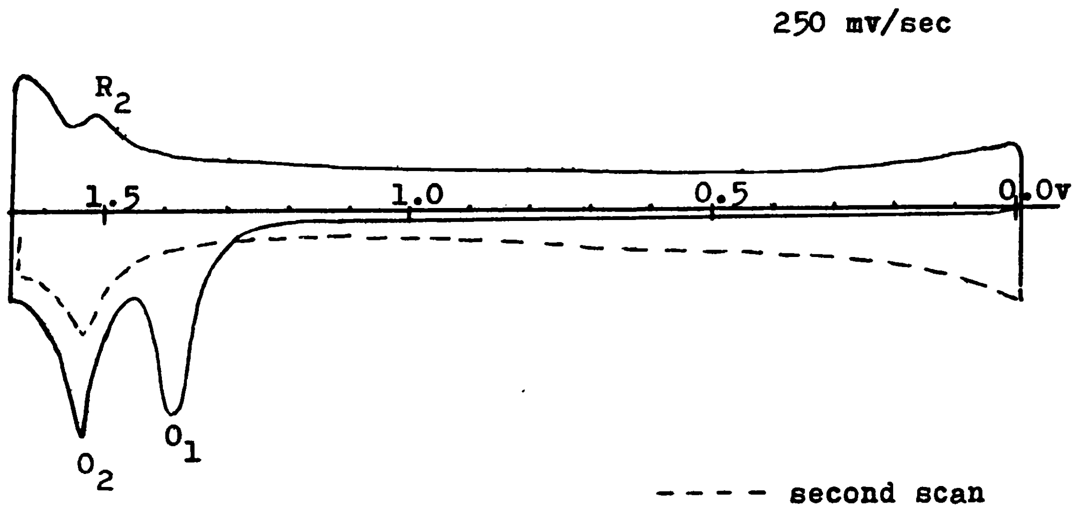
The synthesis of amide (26) followed a similar route to that of the formation of (14), except p-anisaldehyde and m-homoanisylamine formed the starting materials.

The amide was obtained in good yield as a colourless oil, the mass spectrum of which (m/e, 313, M^+) indicated the correct structure, but the interpretation of the ^{1}H nmr was at first confusing (see p. 226). In deuteriochloroform the N-acetyl protons resonated as two singlets at $\delta = 1.97$ and $\delta = 2.09$ as did the methylene protons of the anisyl moiety at $\delta = 4.25$ and $\delta = 4.49$, both doublets having equal intensities. The splitting in the m-homoanisyl fragment was also complicated, but temperature studies in dimethylsulphoxide showed these effects to be due again to slow rotation about the C–N amide bond; however, because the acetyl function was exocyclic to cyclized product we considered that this should not affect the course of the electrolysis.

Anodic oxidation of (26) using a platinum gauze electrode in acetonitrile proceeded with an initial electrode potential of 1.35v (vsSCE) which quickly rose (less than two minutes) to over 2.00v, under-galvanostatic conditions. The electrode was cleaned and replaced, but continuation of the anodic oxidation under potentiostatic control resulted in a rapid decrease of current through the cell. Even removal and cleansing of the electrode in warm concentrated nitric acid failed, the only satisfactory method found was to physically scrape the electrode surface. After a few such cleanings this electrolysis was abandoned. Later attempts in which the electrolyte conditions were changed and pulsing techniques were used, were similarly unproductive.

Cyclic voltammetry of the amide (Fig. 15) showed on

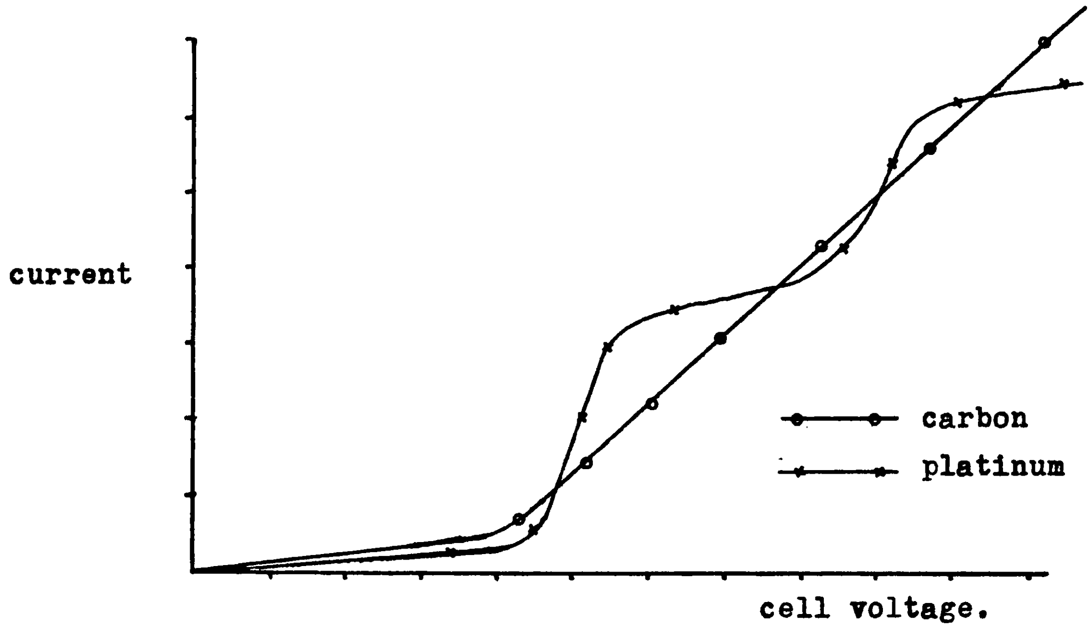
Figure 15



the first sweep an irreversible one electron peak at 1.39v (O_1) followed by a further oxidation peak at 1.54v (O_2) forming part of a couple, the associated reduction peak being much less intense and occurring at 1.50v (R_2). On the second scan, O_1 had disappeared with

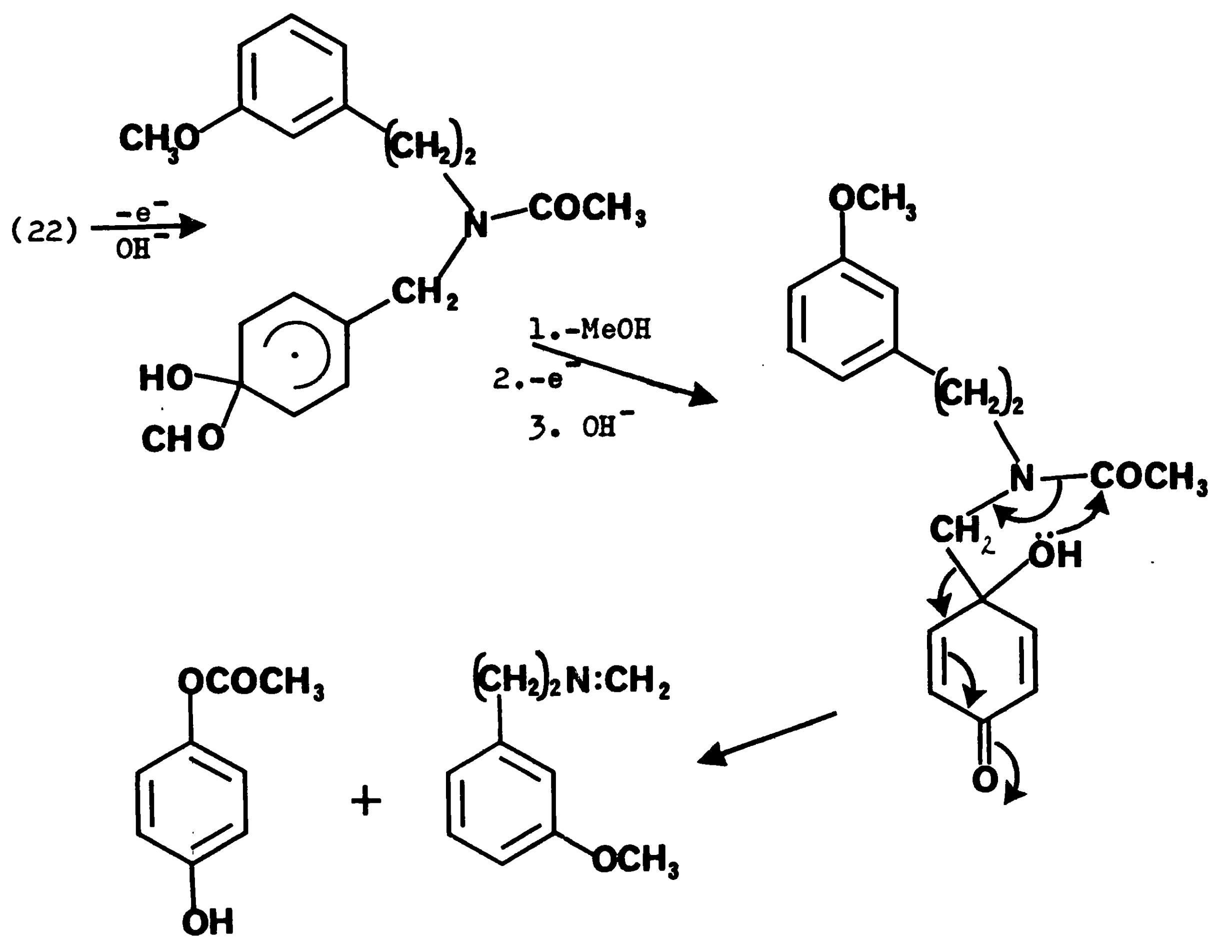
O_2-R_2 much decreased in intensity. Interestingly, after a pause, when the sweep was reset to zero and the initial concentration of substrate around the electrode, restored, further anodic sweeps only exhibited a weak peak at 1.50v, thereby confirming that filming had occurred, and that the electrode was no longer responsive.

The susceptibility of platinum to filming has been noted (ref. 7, p. 200) and this prompted us to examine the anodic oxidation of (26) with a carbon felt anode. Comparing the current/voltage plots (Fig. 16), for this type of system against those obtained for platinum, indicates that carbon is less selective in its oxidative ability, whereas, platinum tends to 'plateau' after each new oxidation potential.



In a preparative experiment with a carbon felt anode the working electrode potential was easily controlled at 1.38v (*vs* SCE) until 2 F mol^{-1} of current had been passed.

Work-up of the anolyte, followed by column chromatography (SiO_2/Ethyl acetate) gave a product which in the mass spectrum showed a molecular ion at m/e 152 (M^+) with a major fragmentation due to the loss of 42 mass units. The infra-red spectrum contained a band at ν_{max} 3400cm^{-1} (OH) and an ester carbonyl band at ν_{max} 1730cm^{-1}. From the analysis of the ^{1}H nmr spectrum it is obvious that this product is simply 4-hydroxyphenylacetate, the signals of the four aromatic protons forming a simple A_2B_2 splitting pattern at δ = 6.60 and δ = 6.80, (J = 9Hz) and the O-acetyl function resonating as a singlet at δ = 2.20. We speculate that it is formed in the following manner:

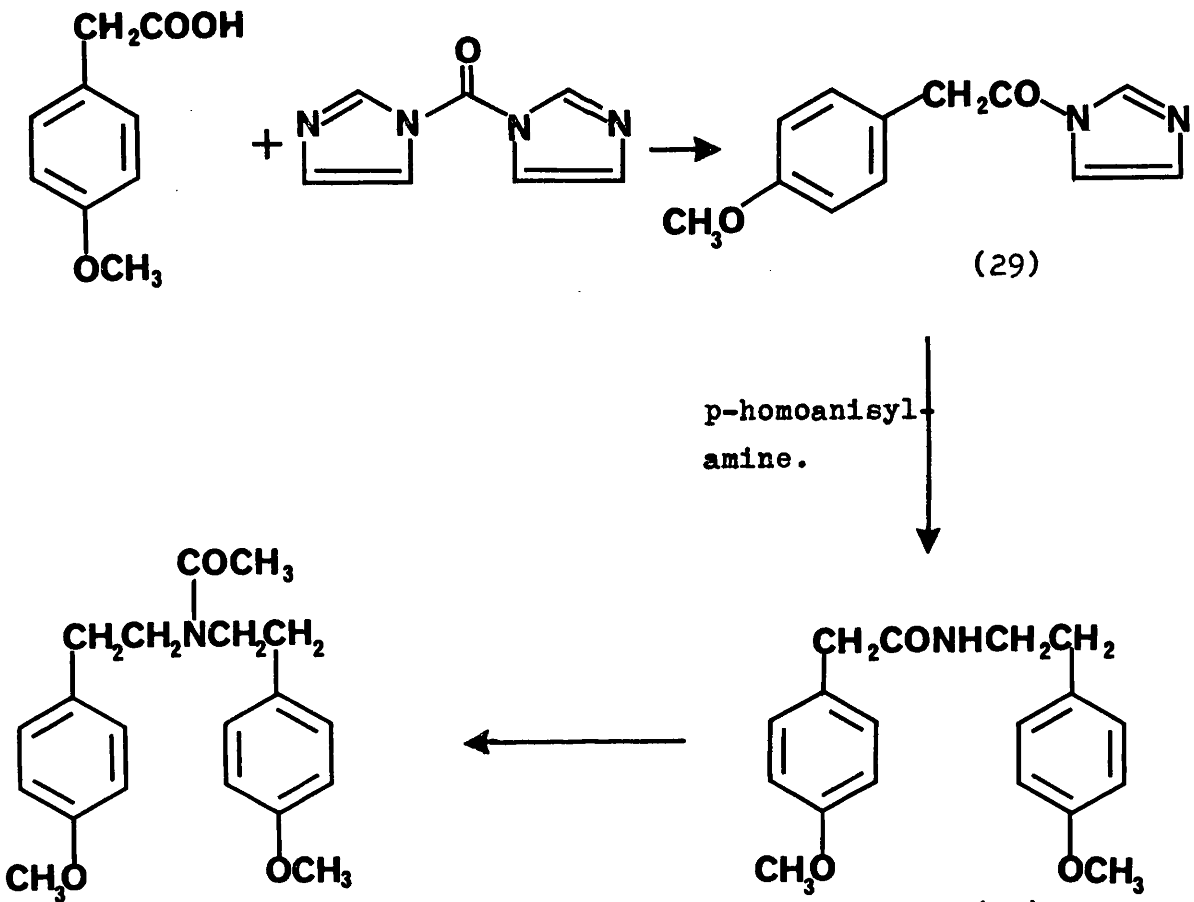


The requirement of water to generate the dienone (28) is not without precedent[36,37], other workers describe similar phenomena, and even though the acetonitrile was dried before use, water concentrations may still be 10mM or higher[38]. No other products were isolated from the work-up procedure and the absence of any intramolecular coupled products was at the time puzzeling, but the probable cause is elucidated in the light of further studies (see chapter 3, p. 166). One further attempt to intramolecularly cyclize a monomethoxylated substrate was undertaken.

<u>Synthesis and anodic oxidation of N-β-(3-methoxyphenyl) ethyl-N-β-(4-methoxyphenyl)ethyl-acetamide (31)</u>

Reaction of p-homoanisic acid with an equimolar amount of carbonyl diimidazole[39] in tetrahydrofuran gave the imidazolide (29). Addition of an equimolar ratio of m-homoanisylamine gave on work-up N-β-(3-methoxyphenyl) ethyl-4-methoxyphenylacetamide[40] (30). We anticipated that reduction of the amide (30) to the corresponding amine followed by acetylation would furnish us with the amide (31), however, prolonged heating under reflux with lithium aluminium hydride (24 hours) in tetrahydrofuran returned only the starting amide, and T.L.C. analysis indicated that some cleavage of the C-N bond had occurred[41].

Brown reports that the use of diborane leads to the facile reduction of amides[42], often where prolonged heating with lithium aluminium hydride gives only poor yields. Reaction of the amide (30) with 1M diborane in boiling tetrahydrofuran was complete in one hour and



(29)

(31) (30)

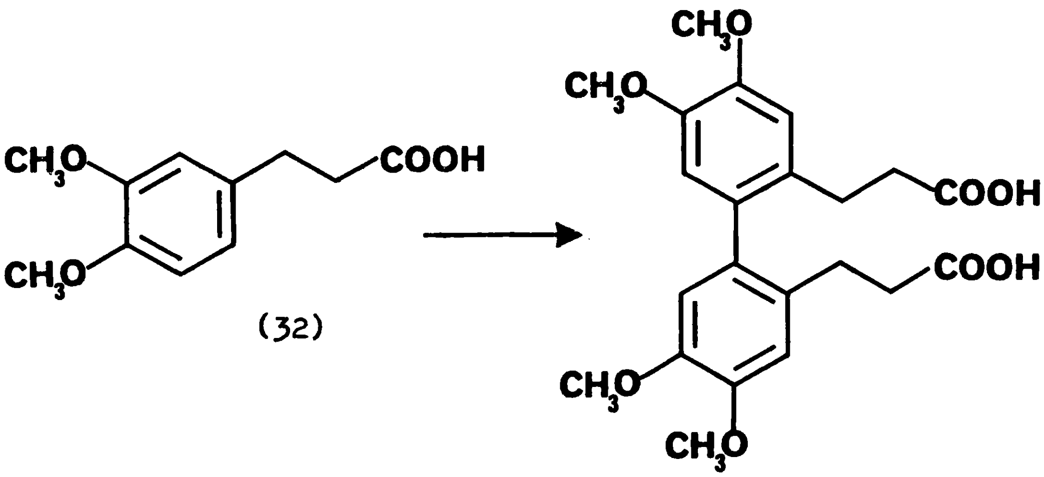
hydrolysis of the resulting boron complex gave the corresponding amine in 92% yield. Acetylation then proceeded smoothly to give the amide (31).

The anodic oxidation of (31) in acetonitrile with platinum electrodes led to the now familiar problem of electrode filming. From our previous experience little success had been achieved by altering the experimental conditions and so we discontinued this electrolysis.

We have stated that anodic oxidation of certain secondary amides resulted in intermolecular coupling, however, in the three amides examined, no products were isolated, this was often due to premature termination of the electrolysis because of electrode fouling, but mass spectrometry of the crude products often indicated that dimeric species were present.

This prompted us to examine the extent of "dimerization" in a simple substrate which could not undergo intramolecular coupling.

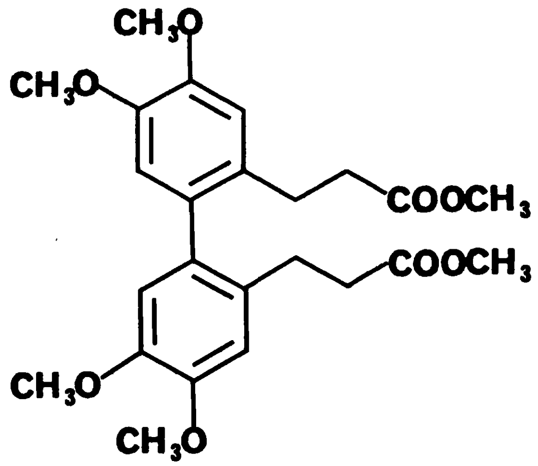
The compound chosen for this study was readily available β-(3, 4-dimethoxyphenyl)propionic acid (32), which underwent electrolysis at 1.10v (vsSCE) without electrode filming until 1 F mol^{-1} of current had been passed. Work-up of the anolyte gave a dark red oil, which when triturated with ethanol afforded a colourless powder (m.p. 140°C).



(32)

(33)

The mass spectrum of this product exhibited a major molecular ion peak at m/e 418 corresponding to the expected dimer (33), but a smaller ion peak at m/e 432 was apparent even after several recrystallizations. In the ^{1}H nmr spectrum, four aromatic protons were observed to resonate as two (2H) singlets at $\delta = 6.63$ and $\delta = 6.84$. The rest of the spectrum, closely resembled that of the starting material, but showed additionally a broad peak at $\delta = 5.60$ which had an integral intensity corresponding to four hydrogen atoms. Since this peak was removed by deuteration it was assumed to be due to two molecular equivalents of occluded water, and indeed when the sample was heated at 115°C <u>in vacuo</u> and the ^{1}H nmr spectrum rerun, this peak was no longer apparent. Recrystallization from 95% ethanol was effective in reconstituting the original substance, but to confirm the structural allocation (33), the dimethyl ester (34) was prepared in 89% yield by reaction with diazomethane.



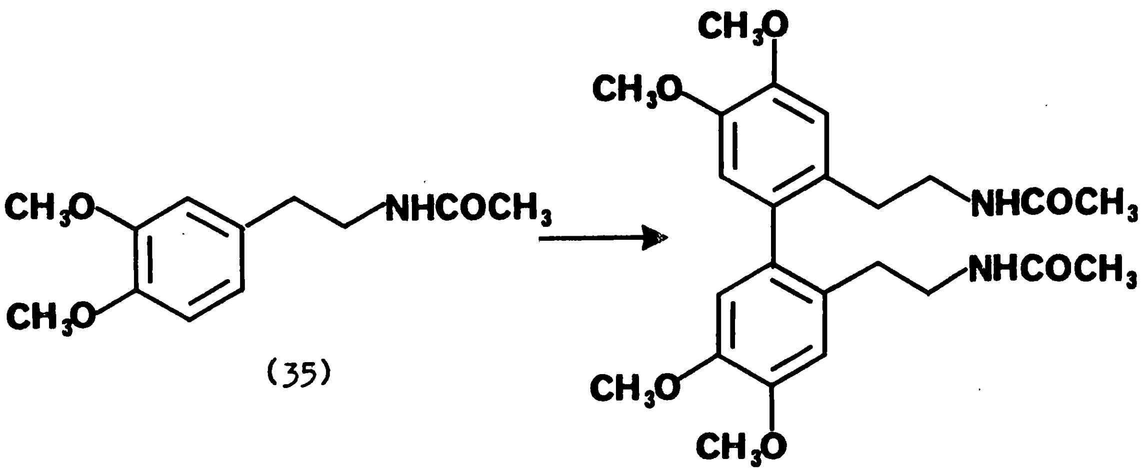
(34)

The mass spectrum of this compound indicated the correct molecular ion m/e 446, and the ^{1}H nmr spectrum showed clearly the resonance at $\delta = 3.65$ due to the six methyl ester protons. The routine testing of both (33) and (34) showed no desirable pharmacological activity.

The yield of the dimer (33) was increased from 30% to 55% by the addition of trifluoroacetic acid to the acetonitrile electrolyte: further evidence of Parker's hypothesis[43,44] that this acid stabilizes radical cations in solution and thus promotes reactions dependent upon their interaction.

At this point we were concerned to see if the nature of the side chain function, would influence to any degree the nature of this potentially useful synthetic route to biaryls and to this end we prepared N-acetyl-homoveratrylamine (35) from readily available materials.

The anodic oxidation of this amide followed a similar course to that of the acid (32), and work-up of the anolyte, followed by column chromatography yielded a colourless powder (m.p. 188-190°C). Mass spectrometry showed a species giving rise to the correct molecular ion (m/e 444) for structure (36) to be present and analysis of the ^{1}H nmr and infra-red spectrum confirmed this structural assignment.



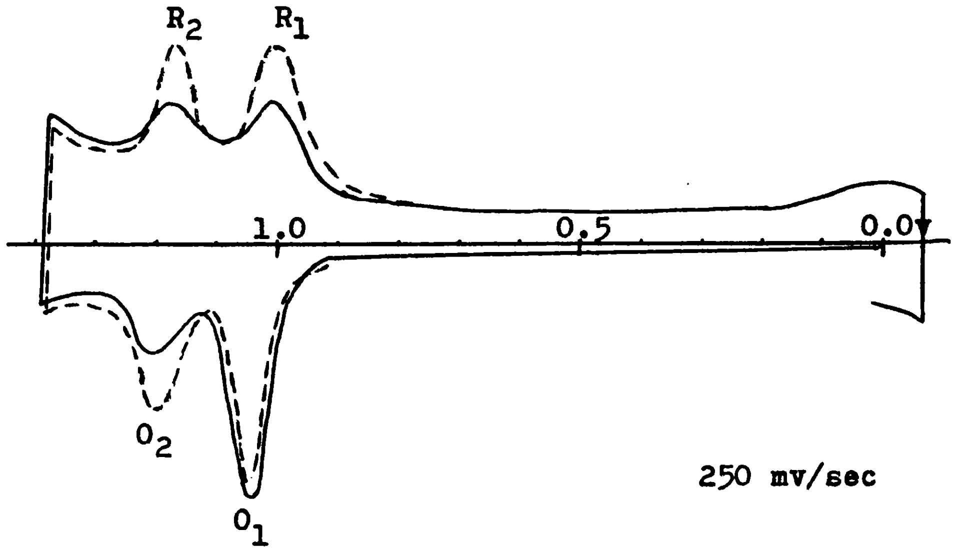
(35) (36)

The yield of the dimer (36) is 26%, which is significantly lower than that for the corresponding acid, but it is conceivable that as the starting acid exists in solution as a H-bonded dimer, anodic coupling to give (33) is a more favoured process.

Cyclic voltammetry of the amide (35), gave on the first cycle an anodic peak at 1.02v (R_1, figure 17), and evidence for a chemical product is gleaned from the redox couple O_2-R_2, the nature of which has not been investigated. The peak height ratio of O_1-R_1 approaches unity at higher scan speeds (ca. 800 mV/sec) indicating that a slow chemical reaction is occurring which is consistent with the observed intermolecular coupling. At slower scan speeds, O_1 is broadened with an integral ratio somewhat greater than that due to a one electron loss. This can be attributed to both oxidation of starting material, together with fast coupling (compared to this slower scan speed) and further oxidation of the product. The addition of trifluoroacetic acid to the cell compartment, has a profound effect, as shown by the dotted line in figure 17.

In the absence of trifluoroacetic acid the cathodic peak R_1 was never as intense as O_1 even at quite fast scan speeds (ca. 600 mV/sec), thus indicating that the initial cation radical entered into chemical reactions relatively quickly: since we believe that "dimer" formation is by comparison slow, this must mean that competing reactions occur (for example, attack by nucleophile,

Figure 17



commonly water[43]). indeed, the low isolated yields of "dimer" support this. By adding trifluoroacetic acid these side reactions are reduced, hence more of the radical cation remains on the reductive sweep and R_1 is intensified. More product is also present, so O_2 is more intense and the oxidized product is stabilised so that in turn, its reduction peak R_2, is also enhanced. The controlled formation of the dimeric species (33) and (36) indicates that the electrode filming problems encountered earlier in this work, could not be attributed to uncontrolled polymerization and so the nature of this problem remained unresolved until later studies were carried out. (See chapter 3, p.166).

CHAPTER 2

The Anodic Oxidation of some simple Heterocycles

The application of anodic oxidation to the biomimetic synthesis of natural products is very attractive, not least because it offers an alternative to the chemically induced phenolic oxidation of aryl nuclei - the key step in the biosynthesis of many plant metabolites[1]. In the field of alkaloid chemistry some progress has been made in using this technique particularly by Kotani and his associates in the synthesis of ($\pm$) colchicine[2] and oxocrinine[3] and also by Stermitz and Miller who have pioneered studies with 1-benzyl-1, 2, 3, 4-tetrahydroisoquinolines leading to morphinandienones[4].

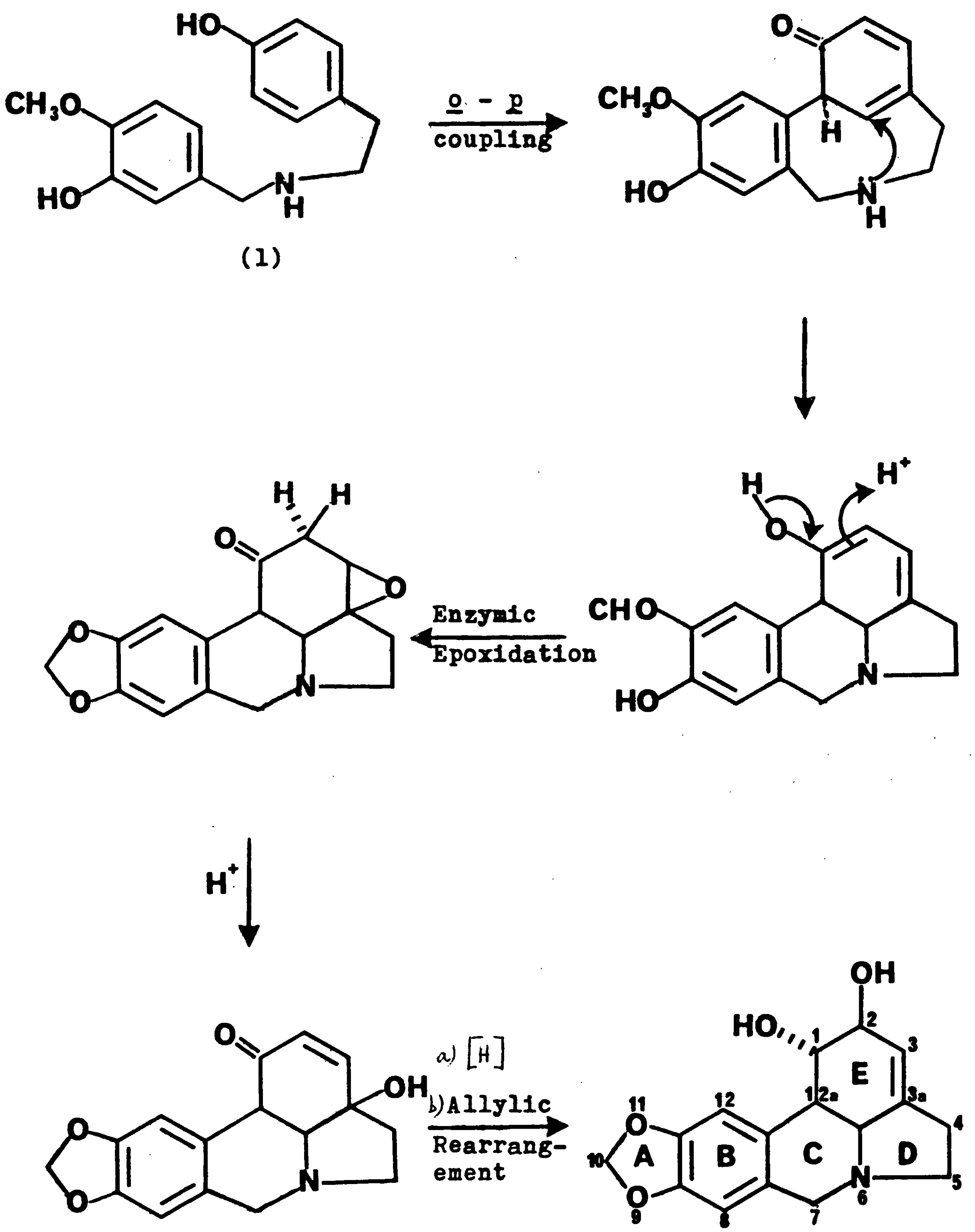
One restriction which exists with anodic oxidation is the same fundamental problem which also adversely affects related chemical methods, namely that <u>para</u>-<u>para</u> coupling to oxygen substituents on the aryl rings is normally preferred. Unfortunately, many desired structures require <u>ortho</u>-<u>para</u> or <u>ortho</u>-<u>ortho</u> union and thus projected syntheses are rendered more complex by the need to introduce blocking groups into the starting materials which must subsequently be removed after coupling.

We felt at the beginning of this work that the alkaloid lycorine (2) the most abundant member of the <u>Amaryllidacea</u> group[5*], might prove to be an interesting and challenging target for electrochemical studies.

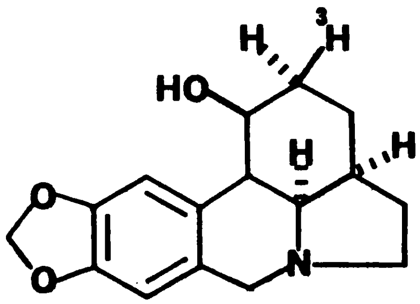
[*] Lycorine has been synthesised, using relays, but the method though technically very sound, is rather tedious[9].

The biosynthesis of lycorine is known in some detail[6] and is outlined below in scheme 1.

Scheme 1



The latter stages require the insertion of an extra oxygen atom in the non aromatic carbocyclic ring and the mechanism shown is based upon arguments presented by Kirby _et al_.[7] and supported by _in vivo_ studies conducted by Wildman[8], who has successfully incorporated labelled (2 -^{3}H)-coranine (3) into lycorine.

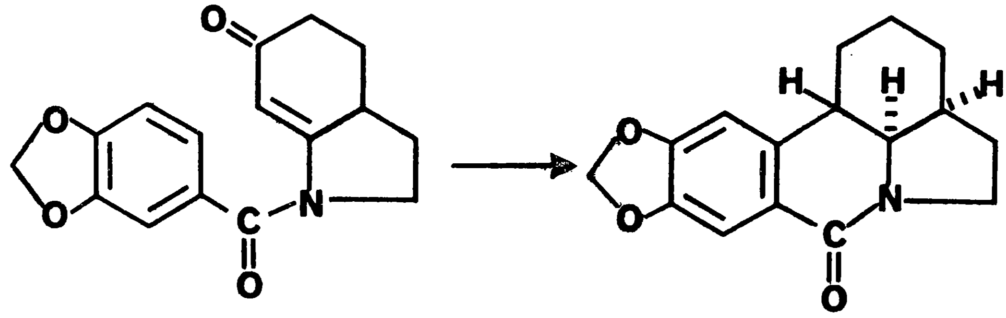


(3)

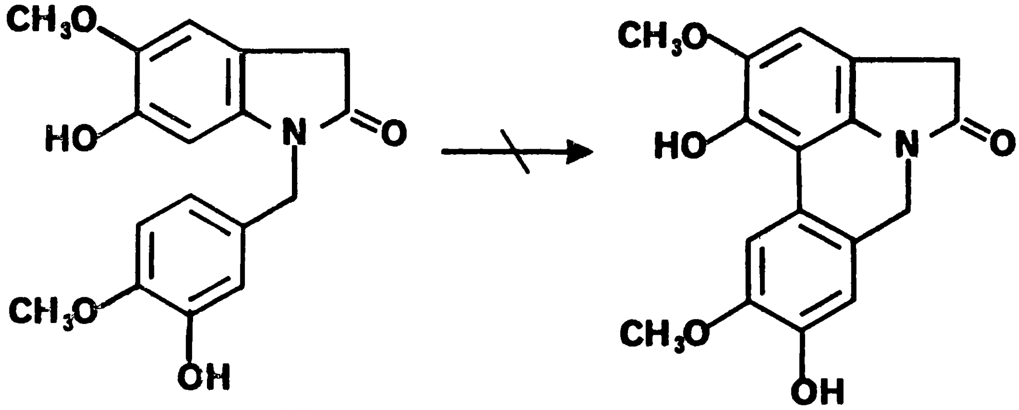
It will be noted that _in vivo_, the primary substrate O-methylnorbelladine (1) undergoes an enzyme controlled _ortho_-_para_ coupling reaction and it is clear from the previous discussion that an _in vitro_ initiation of the natural process would be unproductive.

Some attempts to overcome this problem have utilized substrates with a preformed heterocyclic system; thus Hideo has effected the photocyclization of the enamido-ketone (4) to lycoran (5)[10] and Kametani _et al_. have conducted a phenolic oxidative cyclization attempt upon the N-benzyloxindole derivative (6)[11]. Sadly, although a product was formed, no structure could be assigned to it[11].

This fact we readily appreciate since the manipulation of phenolic substrates under oxidative conditions is

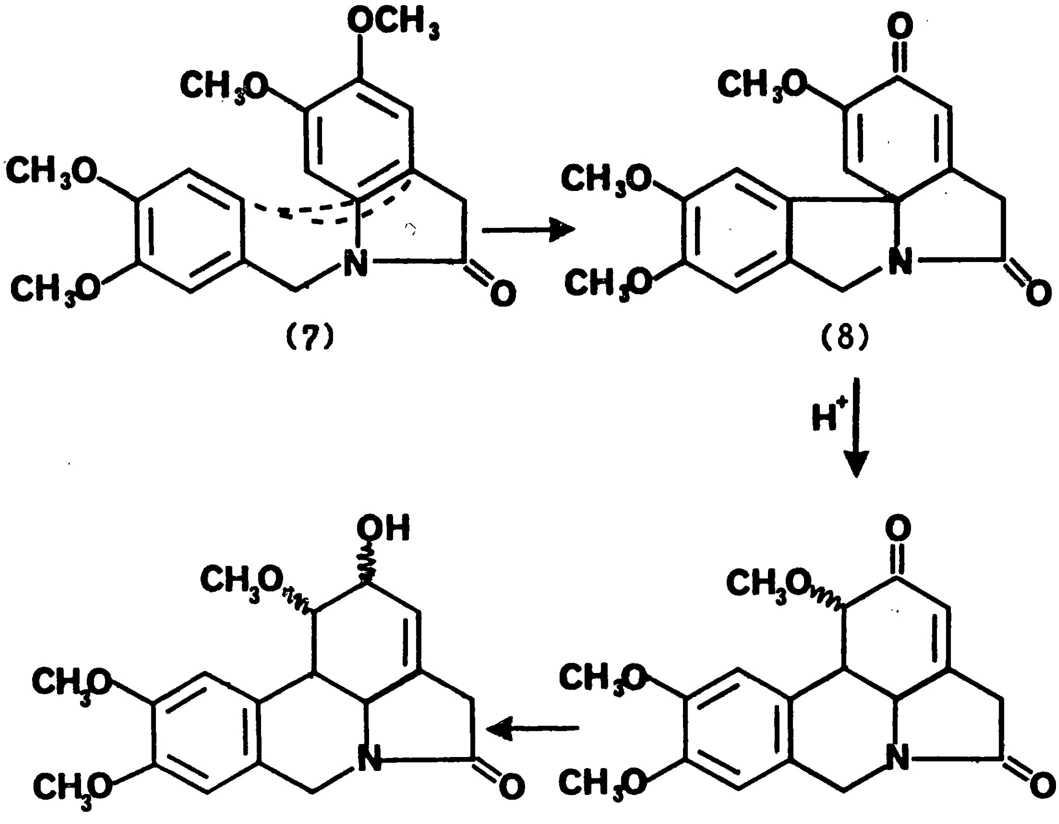


(4) (5)



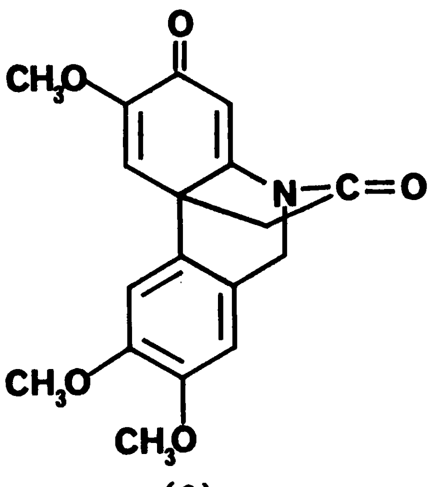
(6)

notoriously difficult, but by using a tetramethoxylated analogue, allowed anodically, we were naive enough to believe we might succeed where the Japanese had failed. We felt that most likely, *para*-*para* coupling of our starting material (7) would occur leading to a product dienone, in this event a dienone phenol rearrangement could be then induced[12]. It is clear , however, that two *para*-*para* coupling modes are possible, one leading to a five and the other leading to a six membered ring system. The former (8) on rearrangement would give rise to a lycorine type structure whereas the latter would not. Possibly the six membered intermediate (9) may be



(7) (8)

judged the more favourable, but an examination of models does not substantiate this view and since the oxidation seemed such a simple reaction to try, we pressed ahead.

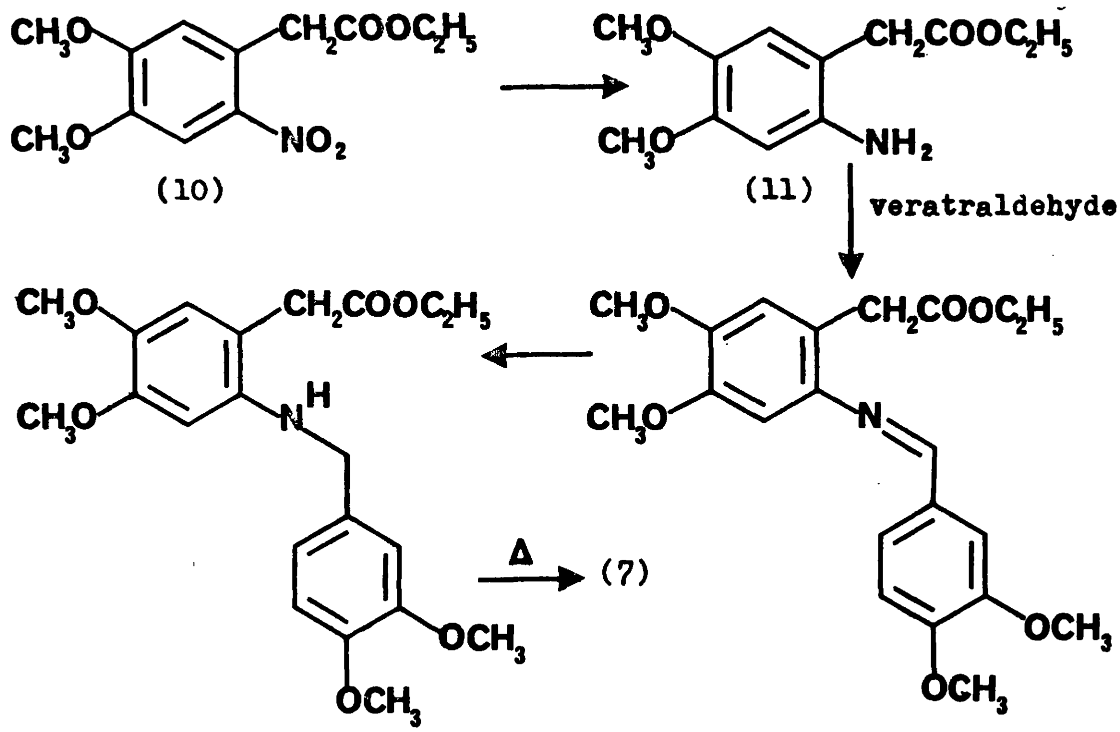


(9)

The projected scheme in fact does have the distinct advantage over the photochemical route of Hideo, that all the necessary oxygen atoms are already present, although the problems of inducing the correct stereochemistry of ring E remains.

<u>Synthesis and anodic oxidation of N-veratryl-5, 6-dimethoxyoxindole (7)</u>

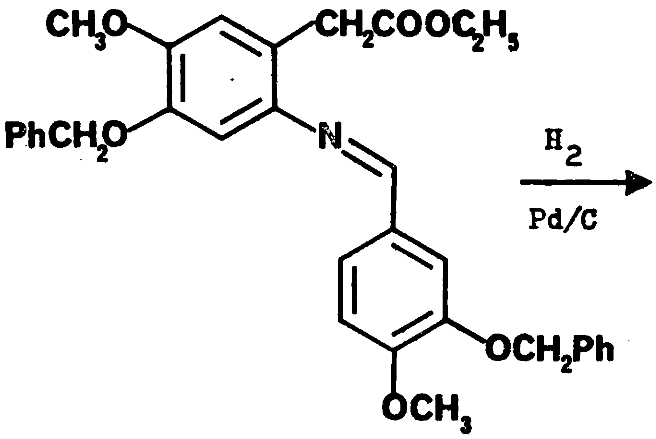
Although this oxindole (7) has not been reported in the literature, we anticipated that it could be prepared by a similar route to that of the phenolic compound (6)[11].



(10) (11) (13) (12)

Nitration of homoveratric acid in concentrated nitric acid afforded 6-nitro-homoveratric acid (m.p.206°C)[13] which was converted into the ethyl ester (10) by heating in ethanol and concentrated sulphuric acid. The amino ester (11) was obtained as a colourless solid (m.p.54°)[14] in nearly quantitative yield through the catalytic hydrogenation of the nitro ester (10) using a 10% palladium on charcoal catalyst and ethanol as solvent. This compound proved unstable when kept for long periods[13], turning into 5, 6-dimethoxyoxindole, however, if adequately cooled it could be kept for several weeks without appreciable decomposition. Condensation of the amino ester (11) with veratraldehyde under azeotropic conditions gave the Schiffs base (12) (m.p.94°), as a reddish brown powder. Attempts to reduce this compound with sodium borohydride in ethanol, gave on "work-up" a mixture of products and T.L.C. analysis indicated that the -C=N- linkage had been hydrolysed, as both the amino ester (11) and 5, 6-dimethoxyoxindole were present. Attempted catalytic hydrogenation of the Schiffs base (12) using a palladium on charcoal catalyst again resulted in cleavage of the -C=N- group, but on changing the catalyst to platinum oxide, the amine ester (13) (m.p.89-90°) was obtained in good yield. This result was surprising, as Kametani reports that reduction of the similar Schiffs base (14) with palladium on charcoal as catalyst led directly to the oxindole (16)[11], though differences between these two catalysts were noted at an earlier stage in the synthesis.

Heating the amino ester (13) in dry toluene for several hours gave the desired oxindole (7) as a colourless powder (m.p.100-101°). Confirmation of the structure was



(14)

deduced from the ^{1}H nmr spectrum which showed a (2H) singlet at $\delta = 3.48$ attributable to the $-CH_2-$ unit of the oxindole ring. A (12H) resonance at $\delta = 3.72$ corresponds to the four methoxy groups and the Ph-$\underline{C}H_2$-N protons resonated as a singlet at $\delta = 4.72$. Mass spectrometry showed the correct molecular ion peak at m/e 343 and the infra-red spectrum revealed a carbonyl absorption at 1705 cm^{-1} consistent with an oxindole unit of structure. The final conversion of the amino ester (13) into the oxindole (7) was only achieved in 35% yield, however, we discovered that on passing (13) through a basic alumina column using chloroform as eluent, conversion to (7) could be effected in near quantitative yield. We suspect this latter transformation is promoted by hydrolysis of the ester linkage in contact with basic alumina, thereby inducing lactam formation.

The anodic oxidation of (7) was carried out in an acetonitrile-sodium perchlorate electrolyte using a platinum gauze anode, and appreciable current flow was obtained when the electrode potential was only 0.80v (vsSCE). From previous experiments, we were aware that this electrode potential was insufficient to oxidize an isolated veratryl unit (typically $E_{1/2}$=1.15v) and so it seemed probable that the oxindole aryl nucleus was being preferentially oxidized. An attempt to raise the electrode potential by increasing the current density necessitated the use of abnormally high currents and so for this first electrolysis the electrode potential was maintained at 0.80v until the starting material had been consumed (in total, this operation involved the passage of 1.80 $Fmol^{-1}$ of current).

On work-up, the anolyte afforded a dark viscous oil and T.L.C. analysis of this crude product (SiO_2, chloroform) showed a continuous trail of unresolved components. Column chromatography (SiO_2, chloroform - pet. ether gradient), as expected, failed to provide any compound in sufficient purity for spectral characterisation. The infra-red spectrum of the crude oil showed broad poorly resolved absorptions at $3500cm^{-1}$, $3300cm^{-1}$, $1700cm^{-1}$ and $1650cm^{-1}$, while mass spectrometry indicated ion peaks in the m/e 680 region, indicating that some dimerization had occurred.

Later attempts in the anodic oxidation of this compound included the use of dichloromethane/trifluoroacetic acid and tetrabutylammonium tetrafluoroborate electrolyte and nitromethane and tetraethylammonium fluoroborate electrolytes[15], as well as the use of high current densities, however, all of these changes failed to give any discernable products.

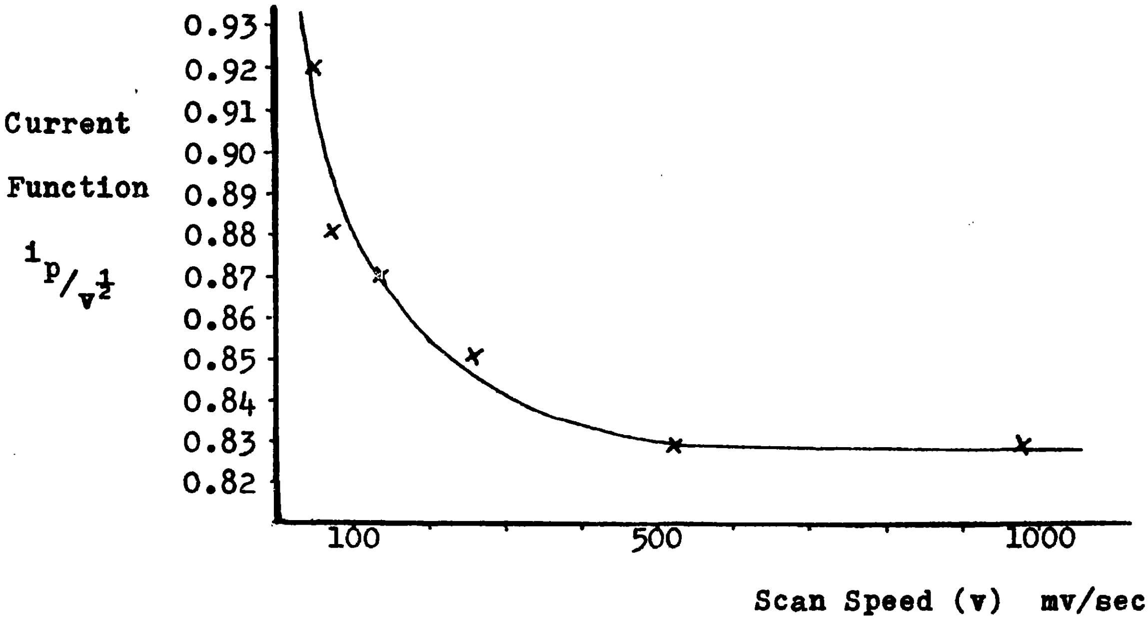
Cyclic voltammetry of the oxindole (7) proved most useful in elucidating the reasons for the compounds apparent instability towards oxidation. On the first cycle at 250 mV/sec an anodic peak (O_1) at 0.70v was observed which was followed by two further oxidative peaks at 1.15v (O_2) and 1.25v (O_3) (Page 239). On the reverse scan cathodic peaks were present at 1.21v (R_3) and 0.68v (R_1) which appeared to be associated with O_3 and O_1 respectively. The oxidative peak O_1 showed some irreversibility if the potential scan was extended to O_3, but remained highly reversible when the switching potential remained below O_3 (Page 239). The measurements of the peak current (ip)* for the first oxidation wave O_1 at various scan speeds are given in Table 1 and a plot of the current function ($^{ip}/_{v^{\frac{1}{2}}}$) versus the scan speed (v) (Fig. 1) is consistent with a slow E.C.E. reaction[16,17].

Table 1

Scan speed	ip	$ip/_{v^{\frac{1}{2}}}$
37 mV/sec	5.6	0.92
66 mV/sec	7.2	0.88
132 mV/sec	10.0	0.87
260 mV/sec	13.7	0.85
525 mV/sec	19.3	0.83
980 mV/sec	26.0	0.83

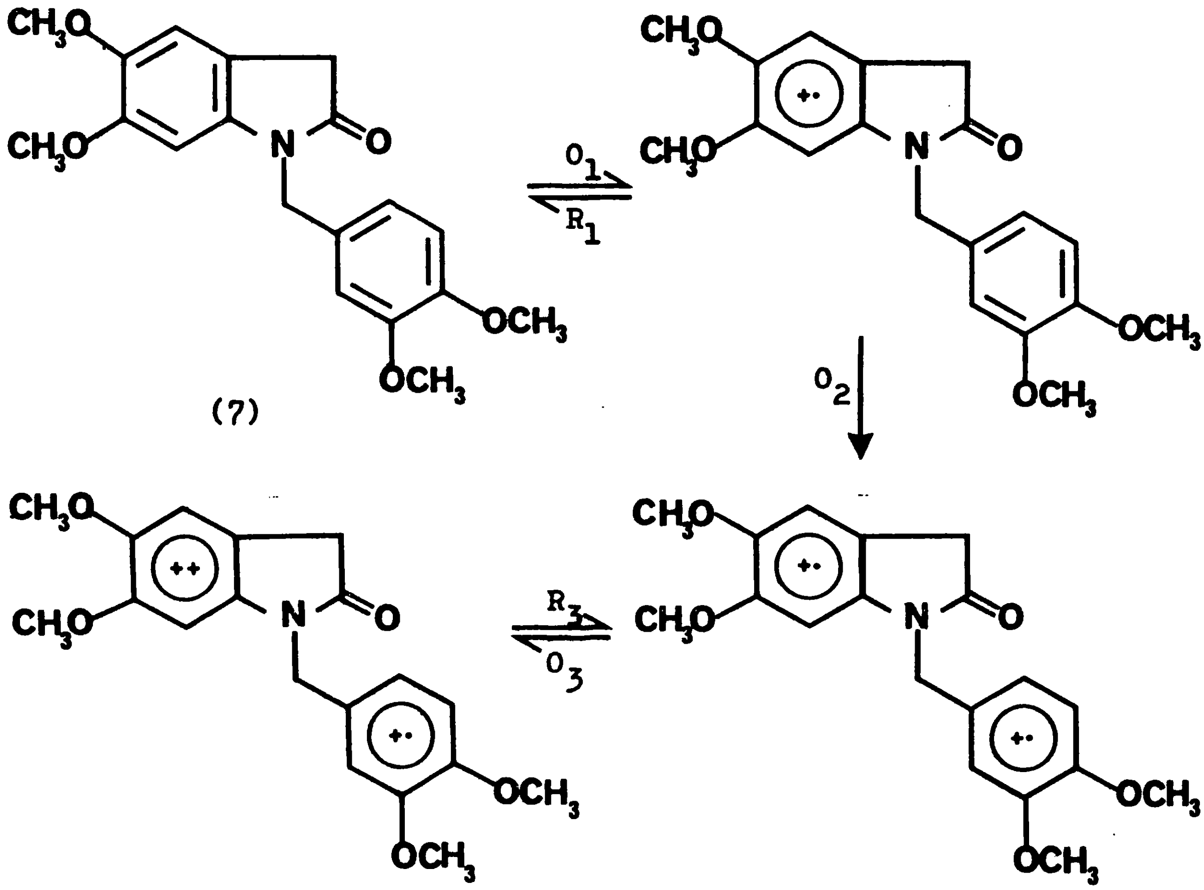
* Although we mention peak currents, no attempt has been made to measure the actual anode current, the quantity being measured is simply the deflection indicated on the oscilloscope, which is of course proportional to the peak current.

Figure 1.



Thus the first oxidative peak (O_1) in the voltammogram corresponds to the removal of one electron (from a comparison with ferrocene which is known to give a one electron reversible transfer[17]) and is attributed to oxidation of the oxindole aryl nucleus. This unusually low value can easily be rationalized when the shape of the orbitals of the nitrogen's lone pair of electrons are considered; effective overlap of the latter with the π-electrons of the aryl nucleus is particularly favoured. This arises because the nitrogen's lone pair of electrons in an oxindole ring are less conjugated with the adjacent carbonyl group than in say acetanilide. This is illustrated by the relatively high carbonyl stretching frequency ν_{max} 1705 cm^{-1}.

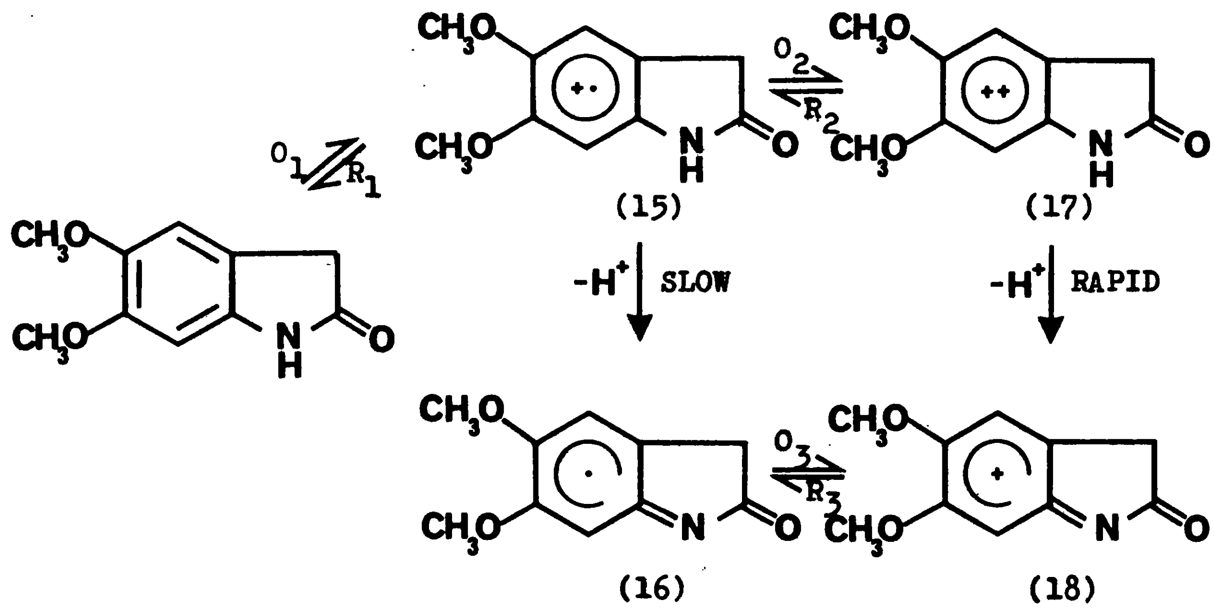
The second oxidation peak (O_2) was largely irreversible even when the switching potential remained below that of peak O_3, this oxidation wave correlates with a one electron oxidation of the veratryl unit. The third oxidation peak (O_3) may be due to the removal of a second electron from the oxindole ring to form a dication as indicated in Scheme 2.



Scheme 2

The suggested formation of a dication is not without precedent, for both Parker[18] and Sato[19] postulate the removal of an electron from a cation radical assuming that the latter is sufficiently stable and the electrode potential is sufficiently high. However, we only felt justified in proposing Scheme 2 after an examination of the voltammetric behaviour of 5, 6-dimethoxyoxindole. On the first anodic scan at 250 mV/sec 5, 6-dimethoxyoxindole reveals oxidative peaks at 0.72v (O_1) and a broader peak at 1.20v (O_2) (Page 240). Whereas the first peak (O_1) was largely reversible at switching potentials below 1.00v giving rise to the reductive peak (R_1) the second oxidative peak gave rise to a much less intense broad cathodic wave (R_2). The addition of pyridine (0.01 M) to the electrolyte, had a profound effect on the voltammogram, almost doubling the peak current for the first oxidative wave (O_1) and reducing its peak potential to 0.61v, and causing the second peak (O_2) to completely disappear. These results are comparable with the findings of Masui et al. who have studied the anodic oxidation of carboxamides[20,21] and are rationalized in Scheme 3. Formation of the dication (17)

Scheme 3



is accompanied by fairly rapid proton loss from the nitrogen (this accounts for the broad and irreversible nature of the peak O_2) to give the imine cation (18). The mono cation radical (15) also shows a tendency to lose a proton at a slower rate: addition of pyridine simply increases the rate of this process and so an E.C.E. reaction is seen at the first oxidative wave. Water also acts in a similar manner but to a lesser extent as demonstrated by the values of the current function ($ip/v^{\frac{1}{2}}$) for varying scan speeds, (Table 2) and a plot of these values (Figure 2) clearly shows the increased rate of the E.C.E. process when water (5% w/v) is added to the electrolyte.

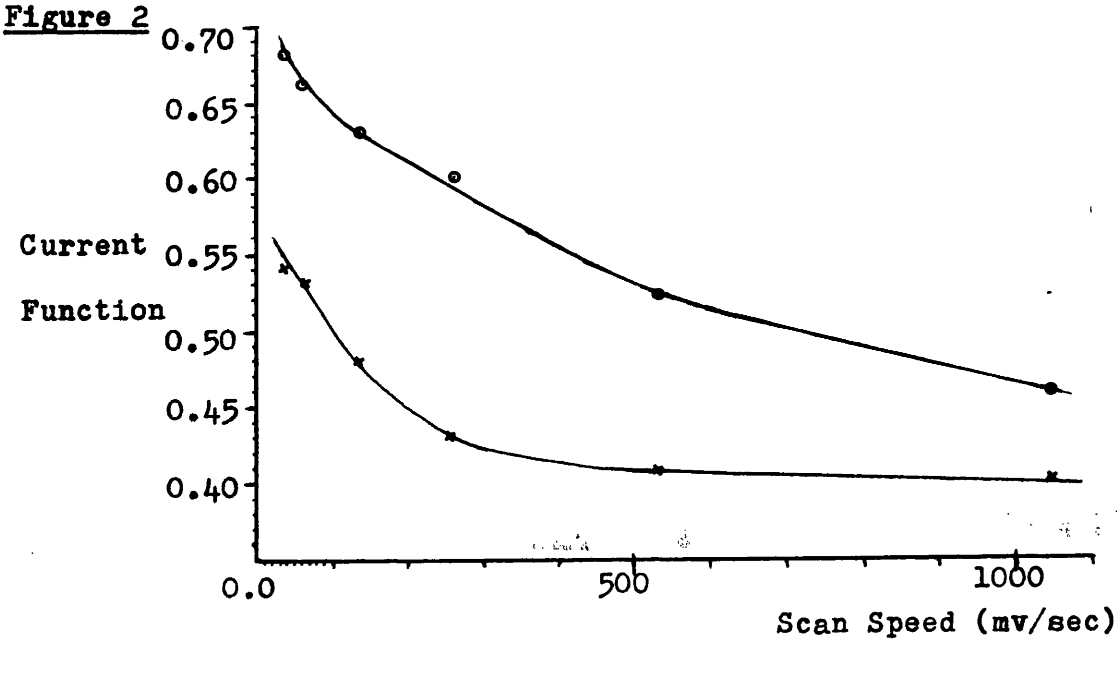
Table 2

Scan speed	ip_1	ip_2	$ip_1/v^{\frac{1}{2}}$	$ip_2/v^{\frac{1}{2}}$
35 mV/sec	3.2	4.0	0.54	0.68
65 mV/sec	4.3	5.3	0.53	0.66
130 mV/sec	5.5	7.2	0.48	0.63
260 mV/sec	6.9	9.6	0.43	0.60
520 mV/sec	9.4	12.0	0.41	0.52
1040	13.0	15.0	0.40	0.46

ip_1 = peak current values in dry acetonitrile

ip_2 = with 5% (w/v) water

Figure 2



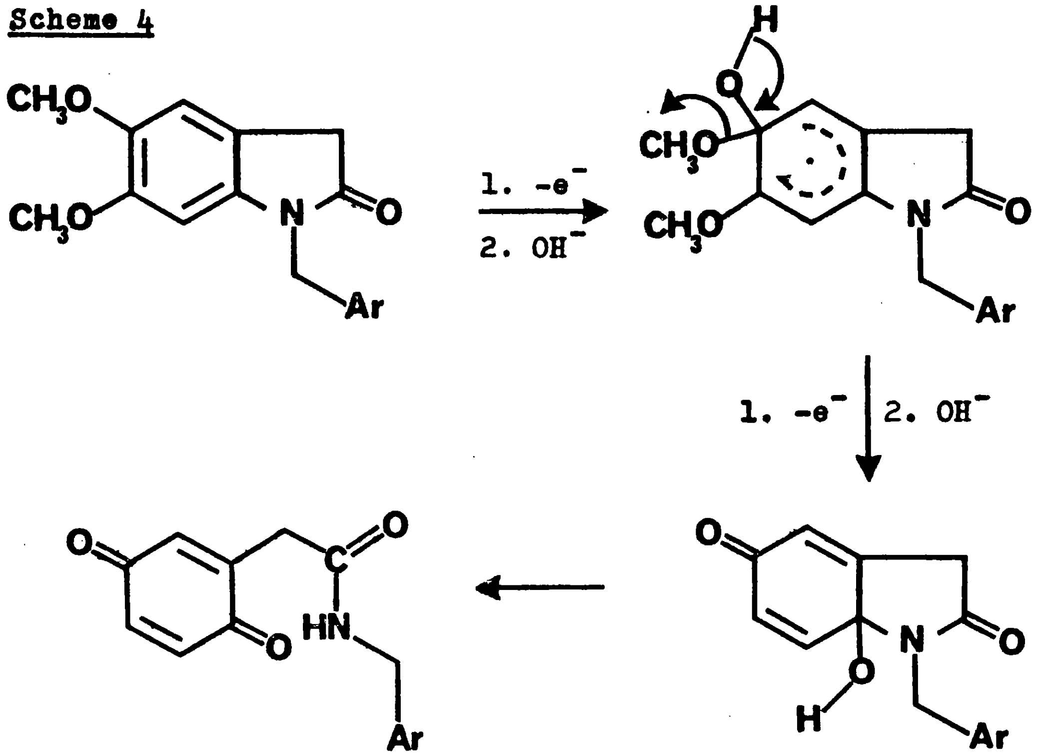
The fact that the first oxidative peak (O_1) shifts cathodically (0.13v) indicates that pyridine is competing for the -N-H of the oxindole ring thereby increasing the electron density on the nitrogen atom[20]. The redox couple O_3-R_3 at 0.40v may be due to the reversible oxidation of the imino radical (16) to the corresponding cation (18) for we know that the oxidation potential of (16) is below 0.61v.

Comparing now, the voltammograms of 5, 6-dimethoxy-oxindole and the oxindole (7), in both voltammograms the initial electron transfer occurs at approximately 0.70v and the second electron transfer peak for 5, 6-dimethoxy-oxindole (O_2) lies close to the third oxidative peak (O_3) of the oxindole (7). Furthermore, the inability of compound (7) to undergo proton loss (as may 5, 6-dimethoxy-oxindole) accounts for the greater reversibility of peak O_3 and hence the voltammogram is comparable to that of N-acetyl-5, 6-dimethoxyoxindole (Page 240) which clearly shows the consecutive removal of two electrons.

During the preparative electrolysis of the oxindole (7), the electrode potential remained at a steady 0.80v and therefore the oxidative breakdown probably followed a modified E.C.E. process (Scheme 4) similar in nature to that described by Masui[21] for the N-methyl-4-methoxybenzan-ilides, although this is not proven.

A similar series of experiments were also conducted with N-piperonyl-5, 6-dimethoxyoxindole, but not surprisingly the results from the anodic oxidation were similar to those

Scheme 4



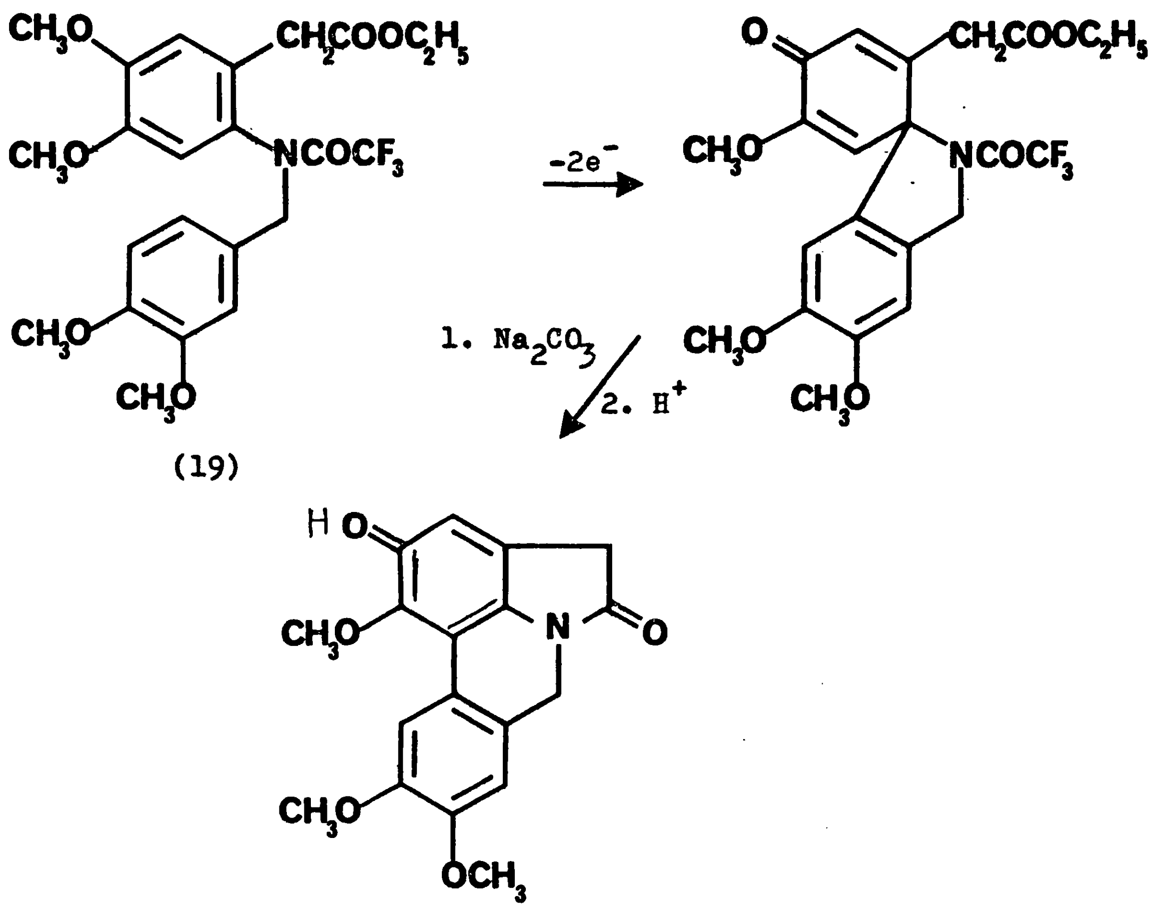
Ar = 3,4-dimethoxyphenyl.

obtained for the oxindole (7).

Clearly, the oxindole nucleus is insufficiently deactivated towards oxidation and so we envisaged that formation of the lactam ring after the initial coupling reaction had occurred might be more successful in furnishing a route to the basic lycorine skeleton. To this end we chose the amide-ester (19) as a suitable substrate for this study and the expected reaction sequence subsequent to electron transfer is indicated in Scheme 5.

The use of the N-trifluoroacetyl function offered two advantages over an N-acetyl group, firstly greater deactivation of the nitrogen is obtained and secondly, the

Scheme 5



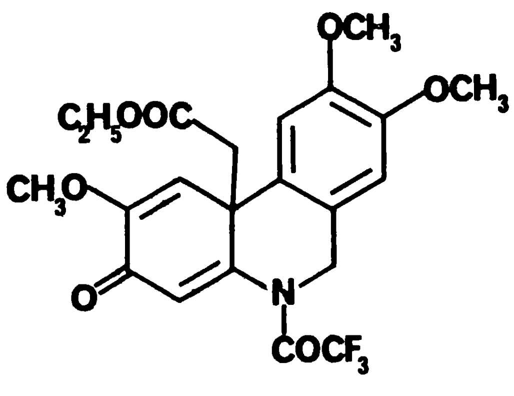
facile removal of this group with weak base[22,23] should allow lactam formation with minimal effect on the dienone system.

Compound (19) was prepared by reacting the readily available amine-ester (13) with trifluoroacetic anhydride in trifluoroacetic acid as solvent.

The anodic oxidation of (19) in acetonitrile and trifluoroacetic acid (10%) with sodium perchlorate as supporting electrolyte proceeded with an initial electrode potential of 1.15v and was continued until 2 F mol^{-1} of current had been consumed. Work-up of the anolyte afforded an almost black amorphous solid and T.L.C. analysis

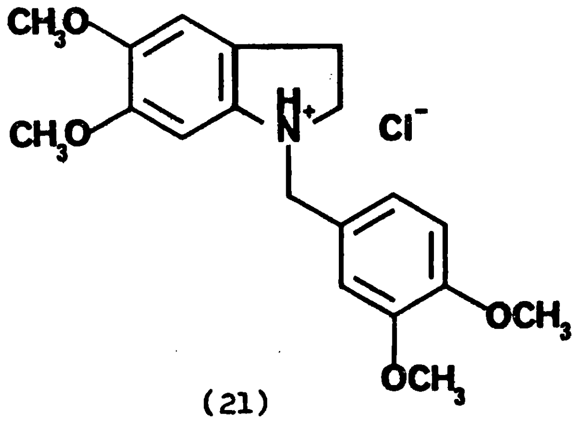
(SiO_2, ethyl acetate) indicated only one major component, with most of the product forming an unresolved trail. Column chromatography gave a small amount of a red oil, but T.L.C. analysis showed the presence of two close running components and so preparative plate chromatography (SiO_2-chloroform) was used to resolve the mixture. The two compounds, however, were isolated in such small amounts that only mass spectroscopic analysis was possible, this showed ion peaks at m/e 426 (M^+) for the two components but it is unproductive to speculate on the possible nature of these compounds at this stage.

On reflection we feel anodic oxidation of this compound would probably lead to the dienone (20) in any case, because molecular models indicate that the absence of the rigid oxindole ring allows para-para coupling to give the alternative dienone (20) which is much less strained.



(20)

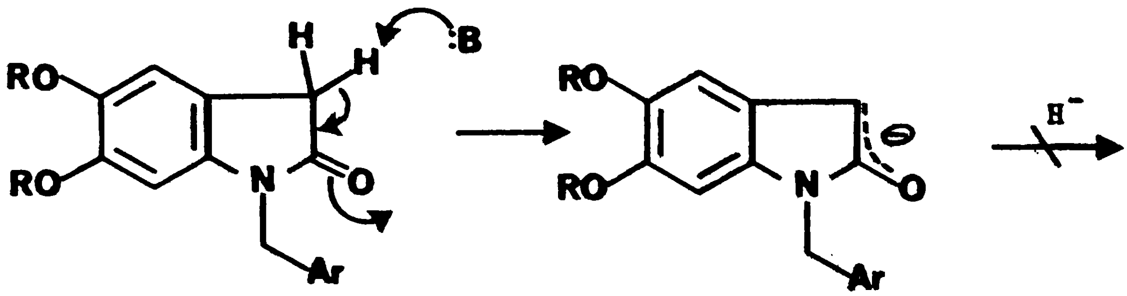
Therefore it seemed likely that in any further attempt to synthesise lycorine-type products, either the oxindole or indoline moiety would have to be retained in the starting substrate. An obvious solution would be to employ an indoline e.g., (21) in which the N atom is quaternized. In this way overactivation of the benzenoid ring fused to the heterocycle is avoided.



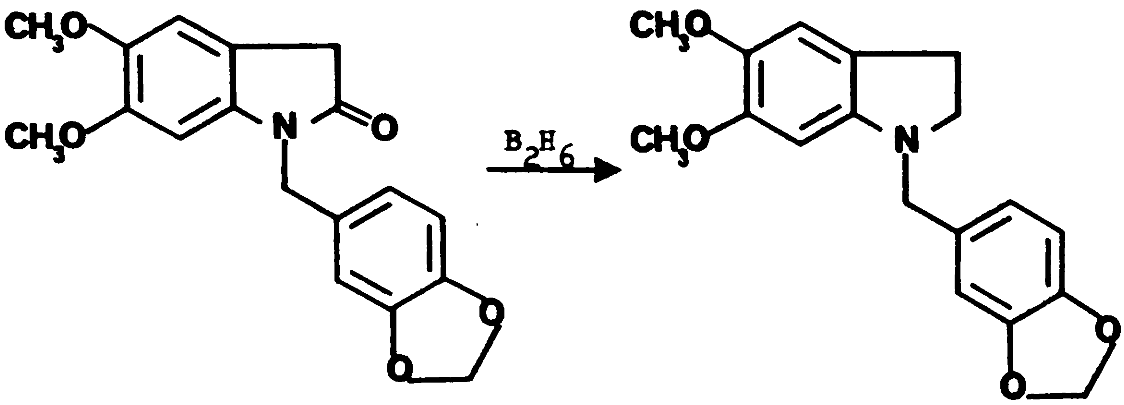
(21)

Synthesis and anodic oxidation of 1-piperonyl-5, 6-dimethoxyindoline (21)

The preparation of N-piperonyl-5, 6-dimethoxyoxindole (22) followed a similar route to that described for the tetramethoxy analogue (7) and was obtained in an overall yield of 52% from homoveratric acid. We anticipated that reduction of this oxindole (22) with lithium aluminium hydride would provide an efficient route to the indoline (21), however, prolonged heating of (22) with lithium aluminium hydride in tetrahydrofuran (up to 12 hours) returned on work-up only the starting oxindole (22). Difficulty in reducing amides with lithium aluminium hydride has been previously noted (Page 95) and seems to be a general area of contention[24]. While it is known that N-H oxindoles are difficult to reduce with lithium aluminium hydride[25], few observations have been made on the difficulty of N-alkyl oxindoles to undergo reduction but we suspect that when there is an acidic proton adjacent to the amide carbonyl function reduction is impeded. This arises out of the dual nature of lithium aluminium hydride (both base and nucleophile): acting as a base, the reagent gives rise to an anion which is resistant to further attack by a hydride ion or its equivalent.



Clearly the use of a "neutral" reducing agent such as diborane should overcome this problem[26] and indeed, facile reduction of the oxindole (22) occurred using

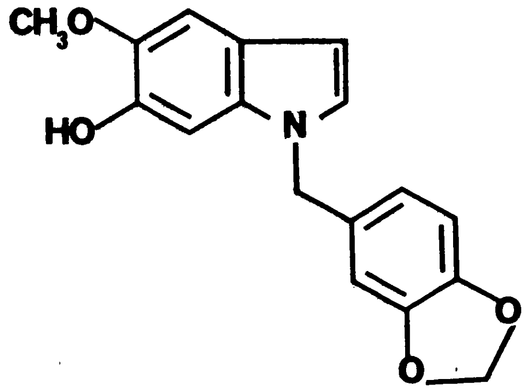


(22) (21)

0.1M diborane solution under mild conditions to give the required indoline (21) as a colourless powder (m.p.71-72°). The ^{1}H nmr spectrum showed two (2H) triplets (J = 6Hz) at

$\delta = 2.90$ and $\delta = 3.28$ indicating the presence of a $-CH_2-CH_2-$ unit and mass spectrometry indicated the correct molecular ion peak at m/e 313.

Attempts to isolate the hydrochloride salt of (21), resulted in the formation of an amorphous solid that was highly hydroscopic and therefore for the purposes of the anodic oxidation, the indoline (21) was dissolved in an ethereal solution of hydrochloric acid; the solvents being distilled off and the product promptly electrolysed in the normal electrolyte. The anodic oxidation proceeded smoothly at 1.25v (vsSCE) until nearly 2 F mol^{-1} of current had been consumed, at which point the anolyte had turned dark brown. Prior to the normal work-up procedures, 2N sodium carbonate solution was added to the anolyte to release the free indoline bases and hence simplify the isolation of the organics produced. Column chromatography of the crude product (SiO_2, ethyl acetate-pet. ether gradient) produced just one pure fraction; a colourless oil which triturated in ether to give a powder (m.p. 90-91°C). Mass spectrometry showed an ion peak at m/e 297 (M^+) with a major fragmentation peak at m/e 135 (corresponding to a piperonyl unit). The ^1H nmr spectrum (Page 227) indicated that only one methoxy group was present, resonating as a (3H) singlet at $\delta = 3.82$. The methylenedioxy moiety was still intact, but surprisingly the indoline $-CH_2-CH_2-$ resonance had disappeared with the formation of two (1H) doublets (J = 3.5Hz) at $\delta = 6.40$ and $\delta = 6.96$. The infra-red spectrum showed a large absorption at $3600cm^{-1}$ (OH) and thus it was apparent that the indole (23) had been formed in an overall 15% yield.



(23)

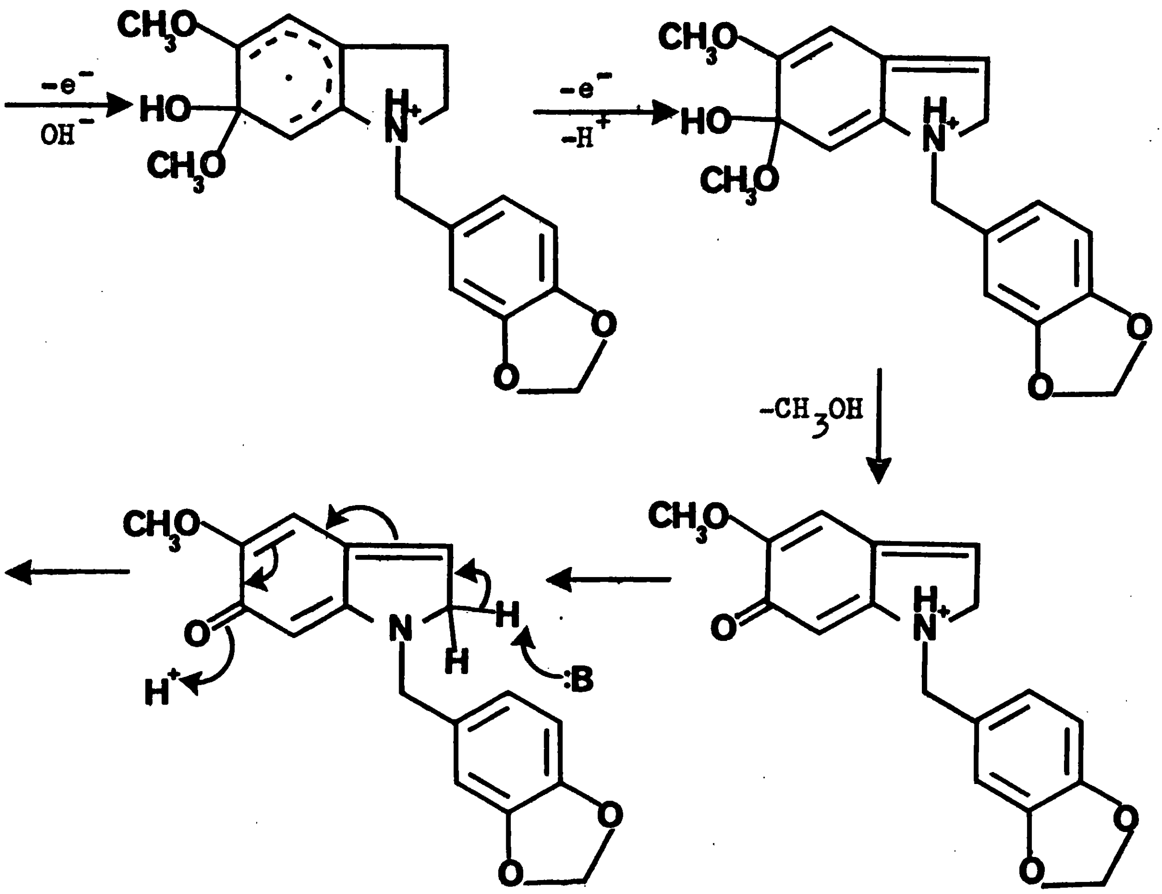
This is the first time to our knowledge that an indoline has been electrochemically oxidized to an indole, a considerable feat, as the indole (23) is extremely unstable to oxidation! However, we have good evidence that (23) is an unavoidable artefact from the work-up procedure that was used, its formation is rationalized in Scheme 6.

The dienone species (24) is almost certainly the product of the anodic oxidation and is formed in a familiar E.C.E.C. type process. This product is then free to undergo a base promoted proton loss from the 2 position of the indoline ring to give the more stable indole (23). The failure of the piperonyl unit to partake in the reaction was at first surprising but cyclic voltammetric studies indicate that it is oxidized at a somewhat higher potential than the quaternized indoline aryl nucleus.

The cyclic voltammogram of the unprotonated indoline (21) shows a total of four anodic peaks (Page 241) at 0.16v (O_1), 0.82v (O_2), 1.31v (O_3) and 1.40v (O_4) at

Scheme 6

(21)



(23)

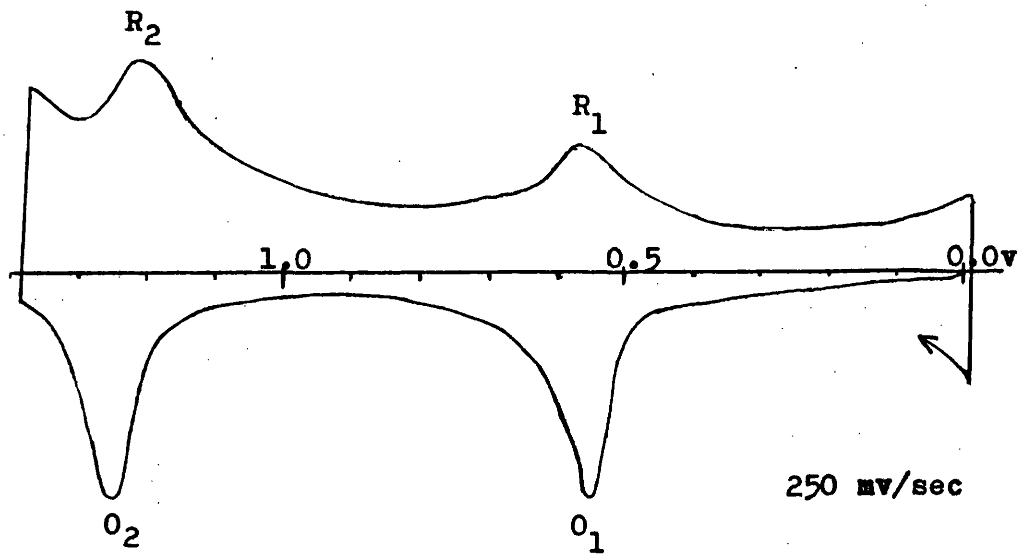
(24)

250 mV/sec. The first two peaks O_1 and O_2 are due to mono cation radical and dication formation of the indoline nucleus. Addition of trifluoroacetic acid to the electrolyte (Page 241) which protonates the indoline nitrogen atom (analogous to HCl) results in the disappearance of these first two oxidative peaks, and only one anodic peak at 1.25v (O_1) with a shoulder peak at 1.31v (O_2) remain. On the return sweep, a reductive wave appears at 1.29v (R_2) which may be coupled to O_2. It is unlikely that trifluoroacetic acid would significantly alter the oxidation potential of the piperonyl unit and so we assume that the shoulder peak (O_2) in this voltammogram corresponds

to the third oxidative peak (O_3) in the voltammogram of the indoline (21). If this analysis is correct, then O_1 must be attributable to oxidation of the indoline hydrochloride fragment, and this oxidation potential difference (0.05v) is sufficient for preferential oxidation of the indoline fragment, but the disparity is not so great as to obviate the possibility of piperonyl oxidation and this may well account for the low yield of product (23).

Cyclic voltammetry of the indole (23) revealed oxidative peaks at 0.56v (O_1) (Figure 3), followed by a second wave at 1.26v (O_2) and on reverse scan, cathodic peaks were present at 1.23v (R_2) and 0.58v (R_1). On the second scan, all four peaks were reduced in intensity and

Figure 3



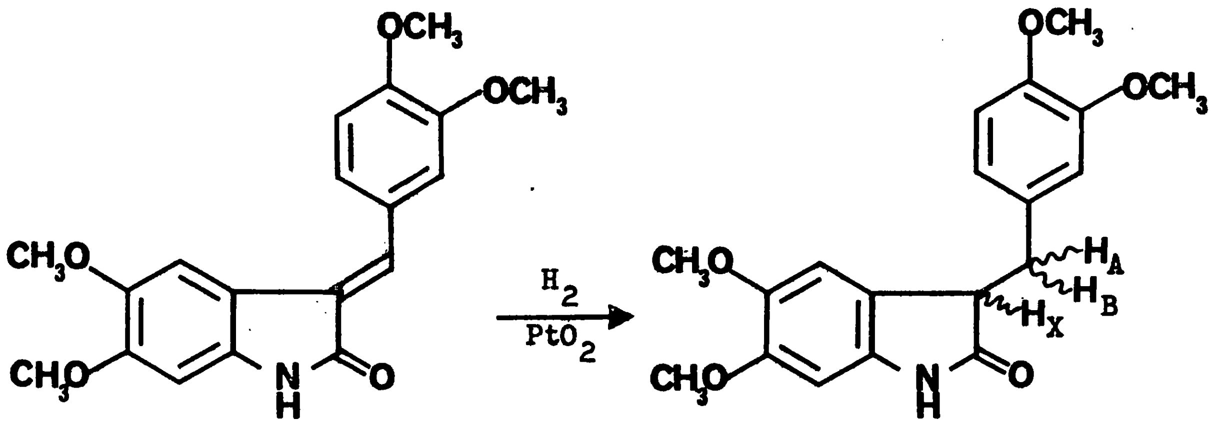
subsequent scanning revealed that severe electrode filming was occurring. This result was not unexpected as it is well known that indoles are unstable to oxidation (indeed the voltammogram of indole shows just one anodic peak at 0.80v which is completely irreversible due to electrode filming). It was on these grounds that we proposed the indole (23) could not have been present, as such, in the anodic cell at an electrode potential of 1.25v.

This result, although successful in regard to potential synthetic organic applications, was a failure in the attempted synthesis of lycorine and at this point we discontinued our efforts in this direction. As a considerable volume of electrochemistry has been reported for the isoquinoline type alkaloids[27-29] we felt it worthwhile to continue our efforts with oxindole and indole based substrates since these have not been studied.

Probing the possibility of coupling an N-veratryl unit with a 5, 6-dimethoxy-aryl moiety resulted in failure; albeit understandable failure; and so it was challenging to see if 3-veratryl-5, 6-dimethoxyindole would behave in the same manner.

<u>Synthesis and anodic oxidation of 3-veratryl-5,6-dimethoxyoxindole[13](25)</u>

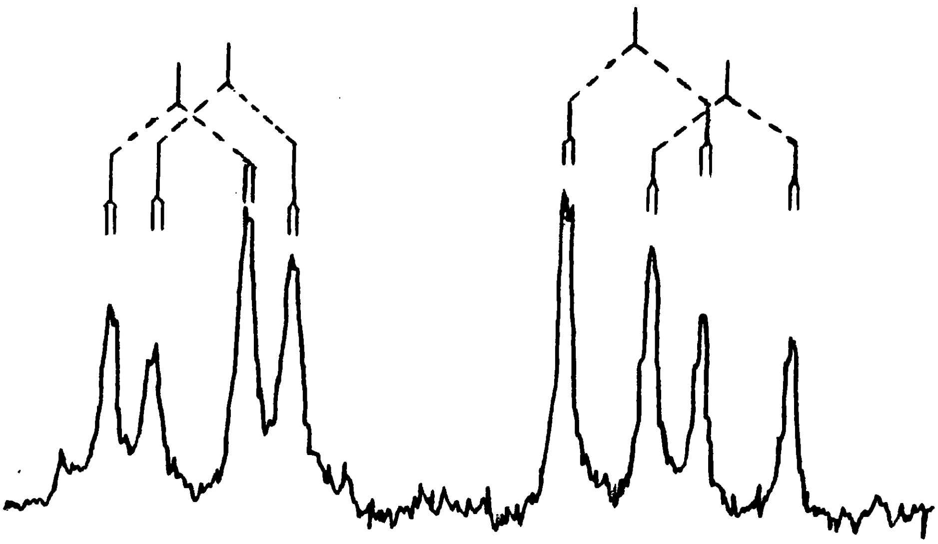
The synthesis of this compound has already been reported by Walker[13] and we found it unnecessary to alter any of the experimental conditions to achieve its production. Thus, 5, 6-dimethoxyoxindole was prepared by catalytic hydrogenation of 6-nitrohomoveratric acid and condensation of veratraldehyde with this oxindole in the presence of pyrrolidine gave the 3-veratrylidene derivative (26) which was converted effectively to (25) by catalytic hydrogenation.



(26) (25)

The ^{1}H nmr spectrum of (25) showed the veratryl $-CH_2-$ unit (Figure 4) as two sets of doublet of doublets (J_{1AB}= 13.5Hz, $\underline{J}_{2AB}$= 13.5Hz); this arising from the fact that the $-CH_2-$ unit is adjacent to a chiral centre and thus the two protons are diasterioisotopic. These signals are broadened due to coupling to the adjacent oxindole proton and we were surprised to find the latter effect was not larger. A value of 3-4Hz would be more usual.

Figure 4

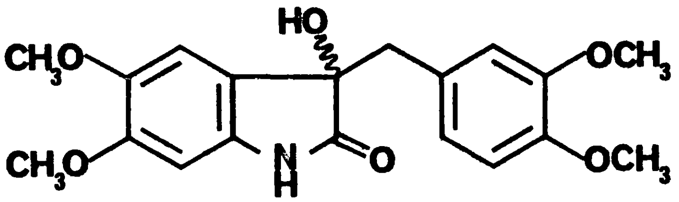


From our experience with oxindoles, we expected the aryl oxindole ring of (25) to undergo oxidation at a lower potential than the veratryl unit, but intramolecular aryl-aryl coupling is not necessarily precluded as electrophilic attack of the oxidized nucleus on a neutral aromatic ring may occur[30].

The anodic oxidation of (25) was conducted at an electrode potential of 0.85v until 2F mol^{-1} of current had been consumed. Work-up of the anolyte, followed by column chromatography (SiO_2, ethyl acetate, pet. ether) gave two colourless compounds, besides a small amount of unoxidized starting material.

Mass spectrometry of the first compound (m.p. 175-176°) showed major ion peaks at m/e 343, 341, 191 and 151 while the molecular ion gave a low intensity peak at m/e 359. The ^1H nmr spectrum showed a 'deuterable' (1H) singlet at $\delta = 2.89$ (Page 228) and two (1H) doublets (J = 13Hz) at $\delta = 3.35$ and $\delta = 4.12$. Four (3H) singlets resonate in the $\delta = 3.70$ region while the five aromatic protons resonate at chemical shift positions similar to the aromatic protons of the starting material. The infra-red spectrum showed two close absorptions at $3350cm^{-1}$ and $3310cm^{-1}$ with further bands at $1710cm^{-1}$ and 1690^{-1}.

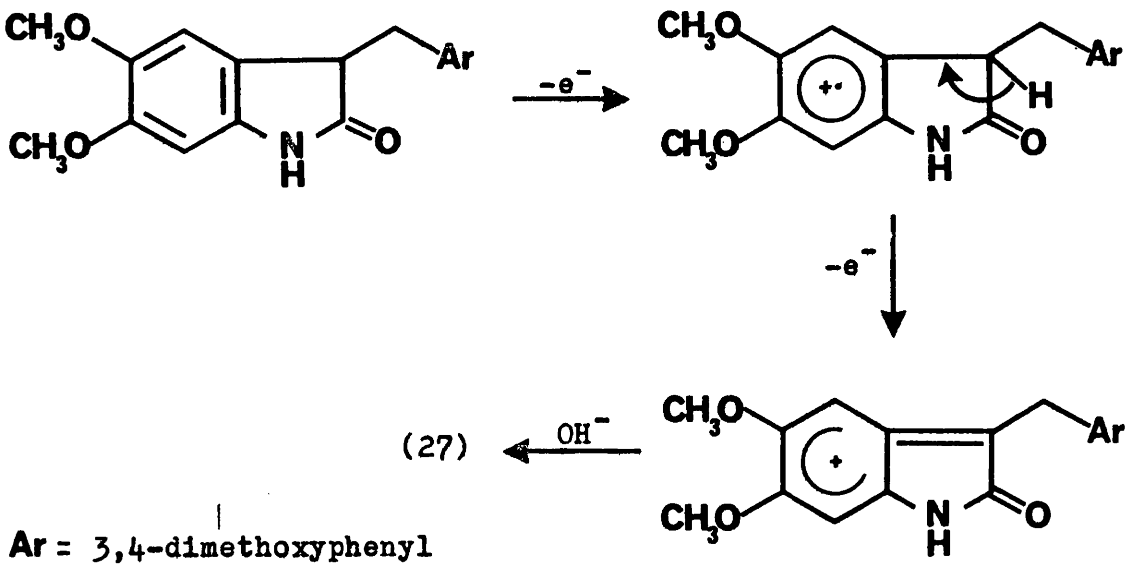
When comparing differences in the ^1H nmr spectrum with the starting oxindole (25) it was apparent that significant changes had occurred in the chemical shift positions of the veratryl $-CH_2-$ unit, the downfield shift suggesting that the nature of the adjacent group had changed. Mass spectrometry indicated a molecular ion 16 m.u. higher than the starting material, almost certain evidence that an oxygen atom has been added. Moreover, both the ^{1}H nmr and infra-red spectra showed an OH group to be present. We conclude that this product has the following structure (27). Thus, a base peak at m/e 151 corresponds to a



(27)

veratryl unit and the weak molecular ion is characteristic of a tertiary alcohol. We speculate that compound (27) is formed by the route shown in Scheme 7, following a simple E.C.E. process.

Scheme 7

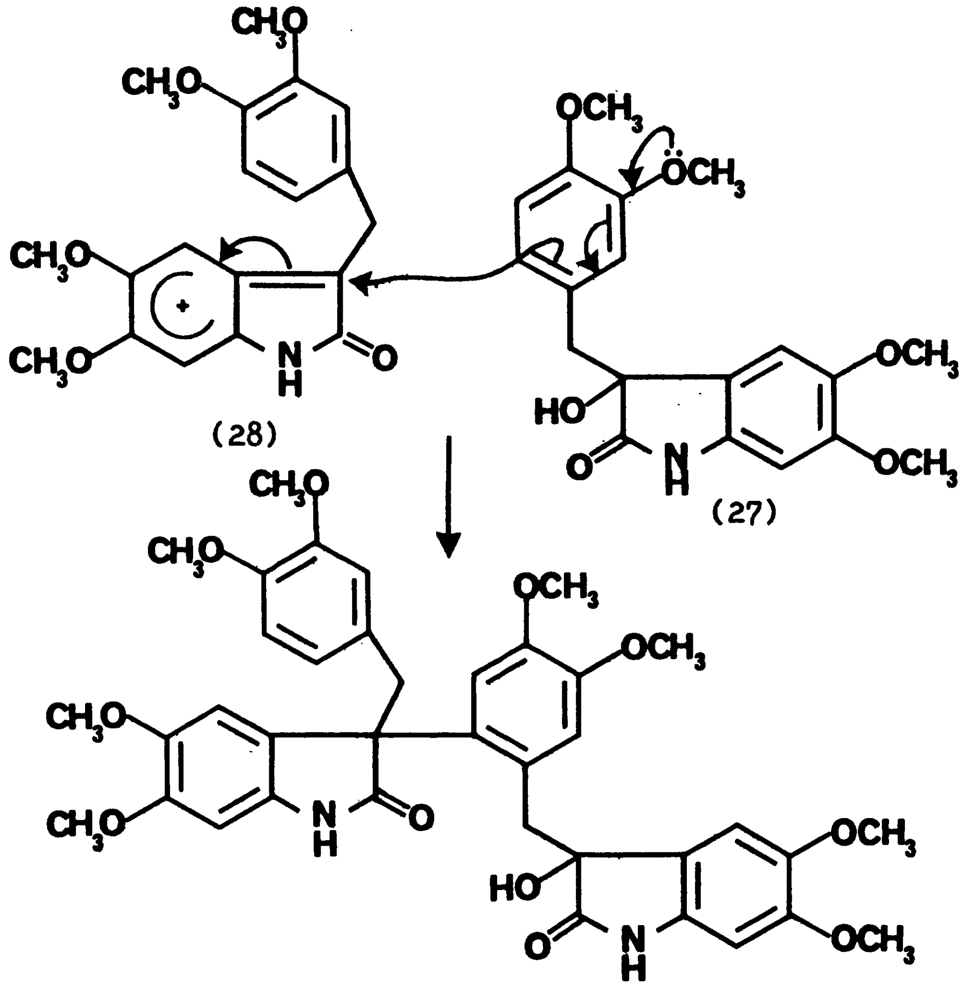


(28)

This result was in some respects surprising, as we had previously assumed that proton loss, after the first oxidation, would occur from the nitrogen, but for this species at least the hydrogen atom attached to the 3-position of the oxindole is lost.

The structure of the second compound (m.p. 271-275°) to be isolated from the anodic oxidation of (25) has proven more problematical, and work was further hindered by the small amounts of material that were isolated.

Mass spectrometry revealed ion peaks at m/e 682, 531, 341, 310 and 220, from this, it was clear that the compound was a "dimeric" species. The ^1H nmr spectrum is reproduced on page 229 . The infra-red spectrum showed absorption bands at 3500cm^{-1} (weak), 3360cm^{-1}, 1705cm^{-1} and 1695cm^{-1} and although mass measurements indicate that a "dimeric" species has been formed, it is clear from the ^1H nmr spectrum that this is not a symmetrical union. The presence of two (1H) doublets (J = 15Hz) at δ= 2.75 and δ = 3.60 is indicative that in one half of the dimer the veratryl $-CH_2-$ protons are non-equivalent, while a (2H) broad singlet at δ = 3.20 shows that the $-CH_2-$ protons are very nearly degenerate in the other half. Furthermore, the ^1H nmr spectrum indicates that only nine aromatic protons are present, establishing that one aryl ring is involved in the point of union, and although with the rather poor integral trace it is not absolutely clear, the count for the aliphatic region also supports this view. On this basis, and a consideration of the multiplicity of the aromatic proton resonances, we propose the following structure (29), which is formed by nucleophilic attack of the veratryl unit of (27) upon the intermediate (28) which has already been forwarded in Scheme 7.

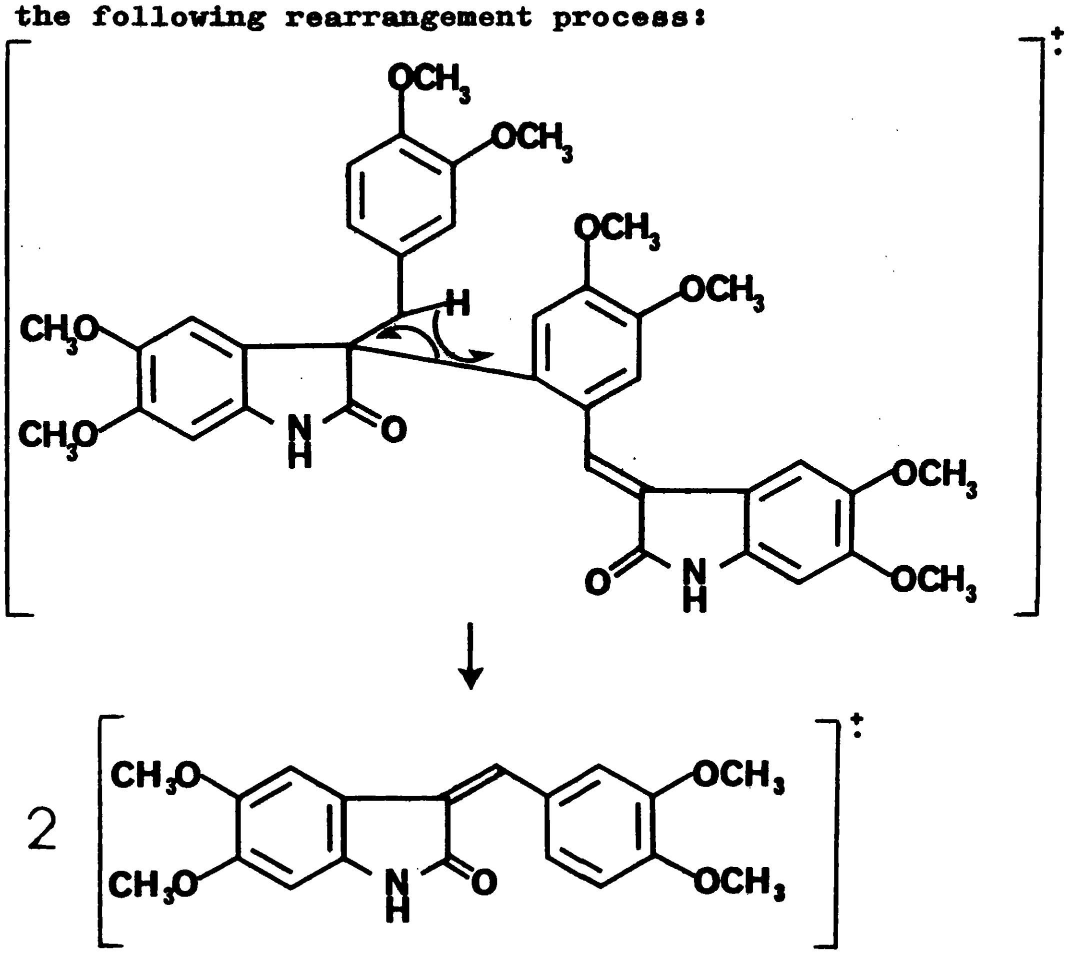


(28)

(27)

(29)

Our proposals rest also on the following additional information: the molecular ion required for this compound m/e 700 is not shown but there is a weak metastable peak at ca, m/e 664.5 in the mass spectrum, suggestive of the loss of 18 m.u. giving the observed ion at m/e 682. The next major loss is of a veratryl unit (giving an ion at m/e 531) but the base peak falls at m/e 341. One may envisage this last cleavage to arise from the m/e 682 ion by the following rearrangement process:



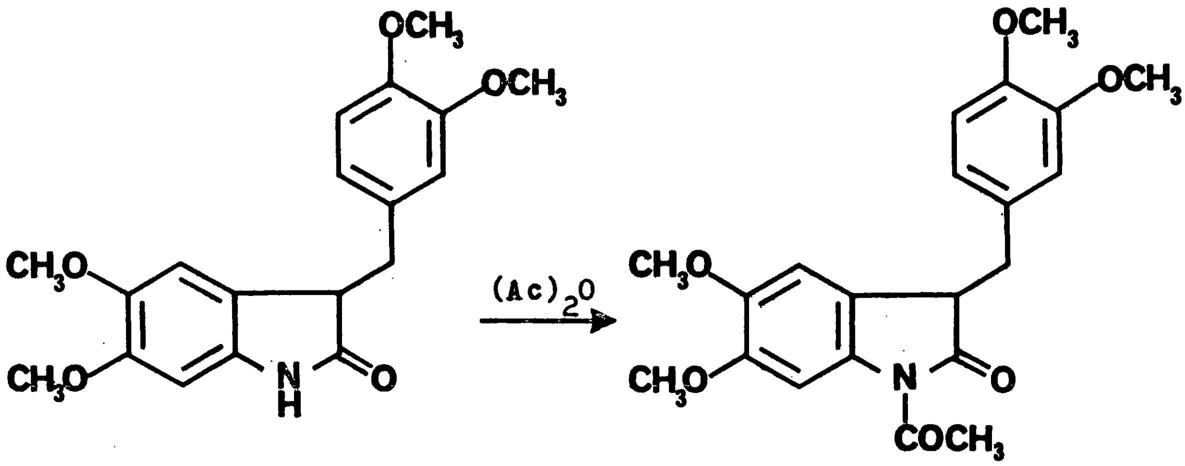
Indeed there is a weak metastable peak at m/e 170.5 which is appropriate to the fragmentation 682 $\rightarrow$ 341. The infra-red peaks at 3500cm^{-1}, 3360cm^{-1} and 3160cm^{-1} correlate with the hydroxyl and N-H functions and there are two low field (deuterable) peaks in the ^{1}H nmr at δ = 7.56 and δ = 7.15 corresponding to two N-H groups. The hydroxyl resonance is at δ = 1.60 and is removed by the addition of deuterium oxide.

Cyclic voltammetry of the oxindole (25) using a platinum bead electrode at 250mV/sec (Page 242) gave an anodic peak ($1e^-$) at 0.71v (O_1), followed by two further oxidative waves at 1.05v (O_2) and 1.25v (O_3) and on the reverse scan showed cathodic peaks at 1.23 (R_3) and 0.70v (R_1). The first oxidative peak (O_1) was highly reversible (at this scan speed) when switching potentials remained below O_3, but the addition of pyridine (.05M) resulted in the peak potential of O_1 falling to 0.61v, with a near doubling of the peak current and the disappearance of O_3. The action of pyridine in this manner has already been described (Page 115) and in spite of the isolation of compound (27) we still believe loss of the N-H proton is more rapid under these conditions than loss of the hydrogen attached to the 3-position of the oxindole ring. (eg. the voltammogram of the oxindole (7) showed no such change on the addition of pyridine). However, there is a more likely formation of product through loss of the 3-hydrogen and so we may have a clash between thermodynamic and kinetic processes, manifested in the formation of (27) and the dimer (29) during the preparative experiment.

<u>Synthesis and anodic oxidation of N-acetyl-3-veratryl-5, 6-dimethoxyoxindole (30)</u>

In an attempt to raise the oxidation potential of the fused aryl nucleus of compound (25), the nitrogen atom was acetylated. We now hoped that the oxidation potentials of the two aryl rings would be sufficiently close for intramolecular coupling to occur. Acetylation of (25) was effected by heating in a solution of acetic anhydride and acetic acid (9:1) for six hours followed by evaporation of the solvents to give the corresponding N-acetyl derivative,

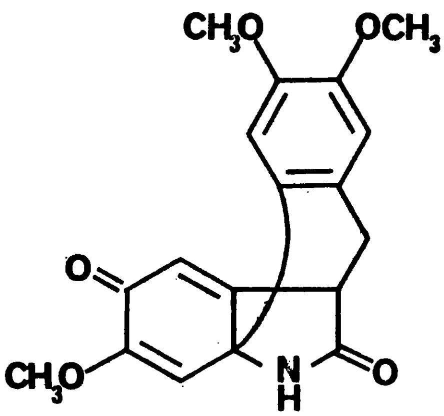
(30) as a pale yellow powder (m.p. 104-105°) in near quantitative yield.



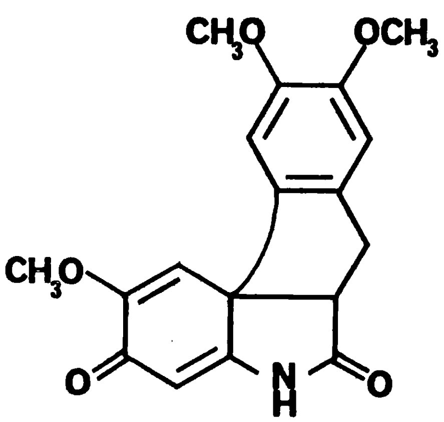
(25) (30)

An inspection of the cyclic voltammogram of the oxindole (30) (page 243) revealed that our attempts to minimize the differences in oxidation potentials between the two aryl nuclei were successful, for only one broad anodic peak at 1.05v (O_1) was present.

The anodic oxidation of (30) in the usual electrolyte in the presence of anhydrous sodium carbonate was conducted at an initial electrode potential of 1.05v (vsSCE) until 2F mol^{-1} of current had been consumed. During the oxidation, the electrode potential fell to 0.85v and the electrode had to be cleaned several times due to a deposit of black material (this layer was not insulating). Work-up of the anolyte, followed by column chromatography ($CHCl_3$-alumina) afforded two pure compounds, the first of which proved to be a small amount of deacetylated starting material (25) probably arising from some unoxidized starting material (30) remaining at the end of the experiment, which could be readily deacetylated through the work-up process. The second component was a colourless powder (m.p. 286-288°) and mass measurements showed a molecular ion peak at <u>m/e</u> 327. The ^{1}H nmr spectrum was remarkably uncomplicated, showing a broad (3H) singlet at $\delta = 3.39$ and three (3H) singlets at $\delta = 3.61$, $\delta = 3.75$ and $\delta = 3.88$, with four further (1H) singlets at $\delta = 5.75$, $\delta = 5.92$, $\delta = 6.50$ and $\delta = 6.84$. No N-H peak was observed in the ^{1}H nmr although the infra-red spectrum clearly showed an -NH absorption at $3310 cm^{-1}$ with further bands at $1740 cm^{-1}$, $1650 cm^{-1}$, $1635 cm^{-1}$ and $1610 cm^{-1}$. These last two absorptions in the infra-red spectrum suggests that olefinic bonds was present, a fact corroborated by the two (1H) resonances in the ^{1}H nmr spectrum at $\delta = 5.72$ and $\delta = 5.92$, the strong absorption at $1650 cm^{-1}$ being due to a carbonyl group. The presence of only three methoxy groups then indicated that a dienone moiety was present and evidence that the veratryl unit had coupled was gleaned from the fact that only two (1H) singlets were present in the aromatic region of the ^{1}H nmr. From this data, two dienone structures (31) and (32) are possible.



(31)

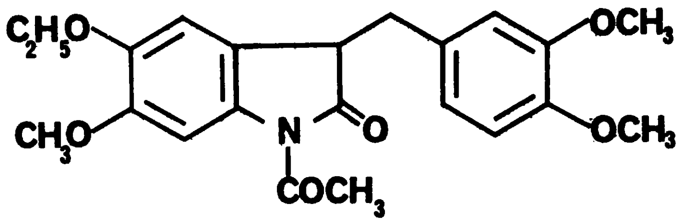


(32)

The abnormally high amide carbonyl absorption ($1740 cm^{-1}$) suggested the presence of a highly strained ring system and to decide between the two alternatives, recourse to an examination of molecular models was made. The union of two five membered rings as in structure (32) results in a rather strained assembly, whereas that between five and six membered rings is much less constrained, and thus one might instinctively favour the first structure (31). Models also show that the hydrogen atom attached to the 3-position of the oxindole ring in structure (31) lies near to the de-shielding zone of the carbonylgroup whereas in the alternative (32) this proton is relatively shielded since it is now very nearly perpendicular to the plane of the amide carbonyl function[31]. In (31) the C-3 proton is allylic whereas in (32) it is adjacent to a saturated carbon atom on one side. Comparison of the ^{1}H nmr spectrum of the product with that of the oxindole (25) shows clearly that the C-3 proton resonance has been shifted downfield in the former and thus we are directed to the structure (31). Attempts to effect a dienone phenol rearrangement reaction by heating the product with mineral acid failed. This too is support for our structural assignment since in doing so, the newly formed six membered ring of (31) would be required to expand to a less stable seven membered array. Structure (32) on the other hand, should rearrange extremely easily.

Absolute proof of the structure could be obtained by the anodic oxidation of N-acetyl-3-veratryl-5-ethoxy-6-

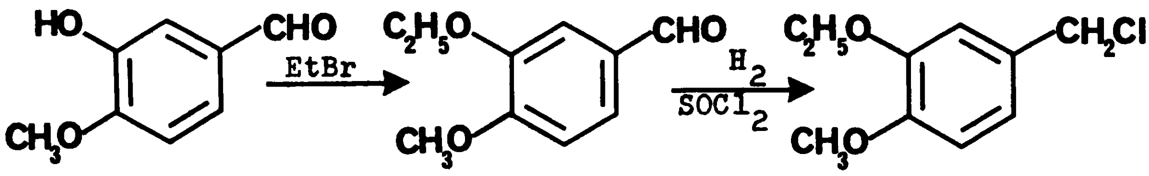
methoxyoxindole (33) as para-para coupling would result in either loss of a methoxy or ethoxy depending on which isomer was formed. However, an attempt to synthesise the



(33)

necessary starting material at this late stage in the work was abandoned when difficulties in preparing 3-ethoxy-4-methoxyphenylacetic acid were encountered.

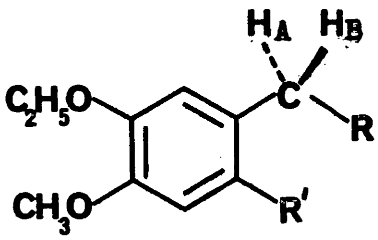
The first three steps in the synthesis proceeded to give 3-ethoxy-4-methoxybenzyl chloride (34) in overall 80% yield from isovanillin, but attempted cyanation of



(34)

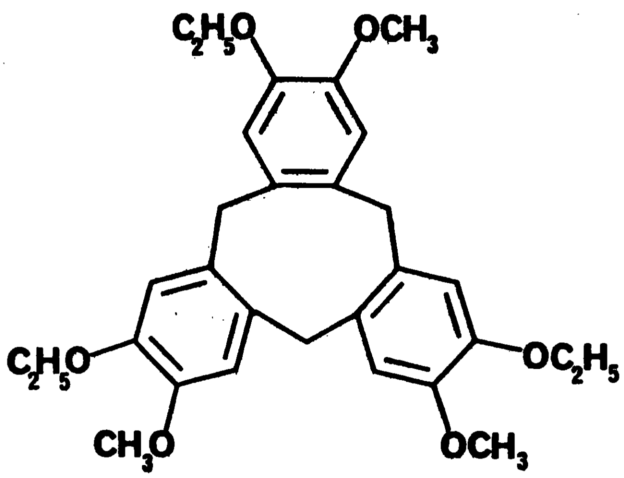
this product with sodium cyanide in acetone in the presence of sodium iodide[32] resulted in isolation of the starting compound (34) together with a colourless powder (m.p. 173-175°). Mass spectrometry of this product gave an ion peak at m/e 492 (M^+) and the infra-red spectrum showed no absorptions above 1600cm^{-1}.

From the ^{1}H nmr spectrum (page230) it was apparent that an equal number of methoxy to ethoxy groups were present and the integral ratios suggested that for every two aromatic protons there was one methoxy group. The two doublets (J = 14Hz) at δ=3.50 and δ=4.68 must be attributed to geminal interactions of inequivalent hydrogens forming a methylene link, and hence a part structure can be drawn.



The ion peak at m/e 492 corresponds to a combination of three of the above units and from the simplicity of the ^{1}H nmr spectrum the molecule must be a symmetrical "trimer". Molecular models show that the structure (35) fulfills these requirements, forming a rigid "crown" type structure which forces the three groups of methylene protons into close proximity, thus imparting the observed inequivalence of these signals.

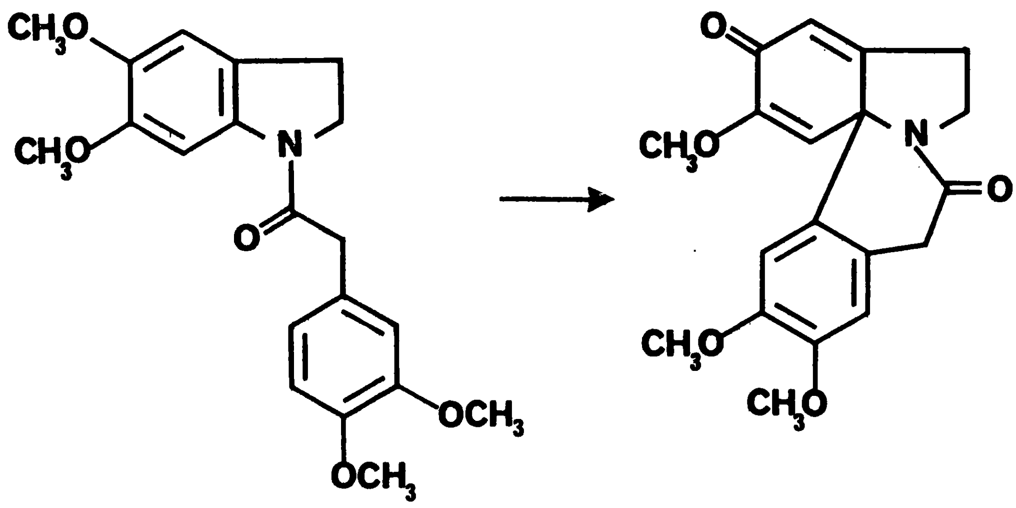
A literature search showed that tricyclic structures of this type have commonly been reported, and Lindsey[33] has prepared (35) (or an isomer of) by the condensation of 2-ethoxyanisole with formaldehyde, although mention is made of the fact that these compounds may be prepared by the action of acid on the substituted benzyl chlorides.



(35)

<u>The synthesis and anodic oxidation of N-homoveratroyl-5, 6-dimethoxyindoline (36)</u>

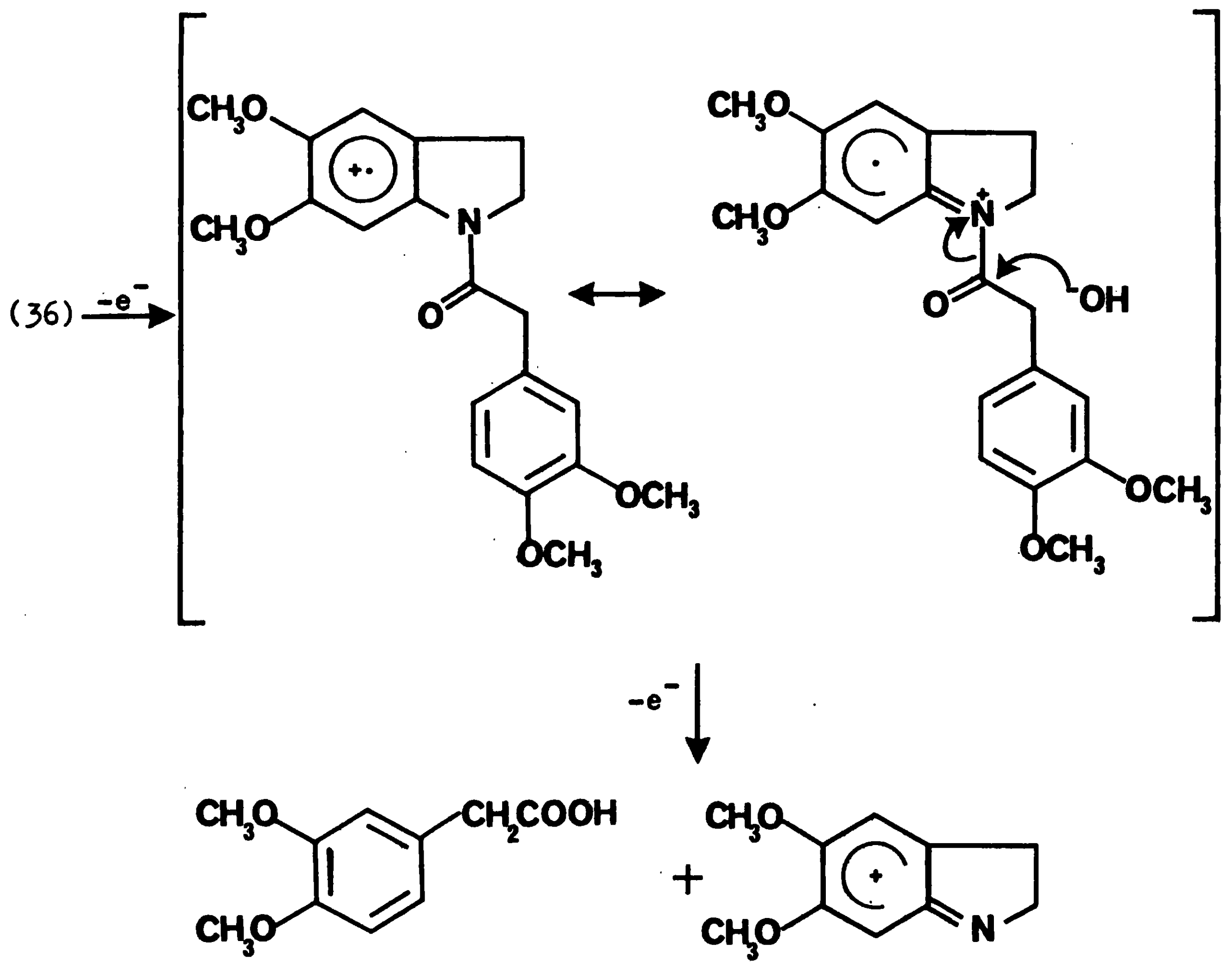
The resultant ring strain of the five membered ring of (8) (page 106) could be considered as an inhibiting factor to its formation. Therefore, synthesis of the indoline (36) which would give a six (or seven, depending upon the position of coupling) membered ring on <u>para</u>-<u>para</u> coupling would overcome this problem.



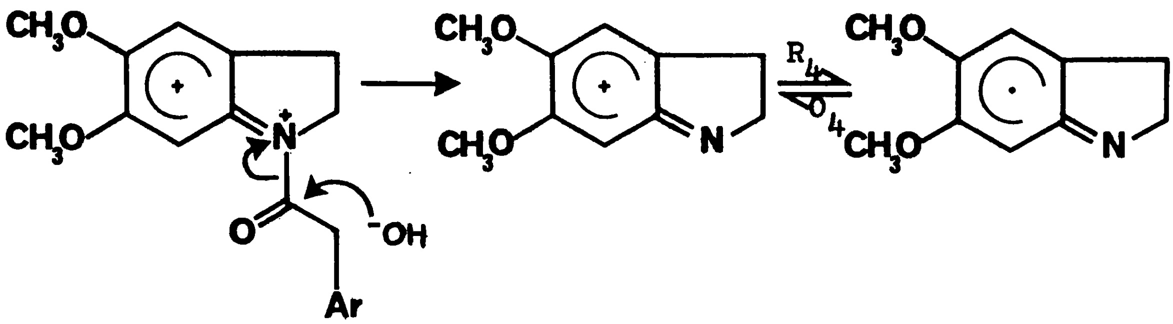
(36)

this scan speed. The new cathodic peak at 0.35v (R_4) was due to reduction of a secondary chemical product and interestingly was only present after O_3 had been scanned. Continuous cycling produced noticeable changes in the voltammogram, with the cathodic peak (R_4) becoming more intense and a new oxidative peak at 0.35v developing.

The anodic oxidation of (36) was conducted at an electrode potential of 0.80v until 1.6F mol^{-1} of current had been passed (monitored by T.L.C. analysis). The only product obtained after column chromatography was a small quantity of homoveratric acid and its formation is outlined below.



The above scheme is almost certainly not a major reaction pathway as only a 5% yield of homoveratric acid was obtained. However, there was good evidence that an imine cation is an unstable intermediate during cyclic voltammetric measurements. The formation of the dication (37) at 1.25v is probably accompanied by a rapid attack of water on the amide carbonyl group to give the imine cation (38). The reversible reduction of this species may well account for the peak R_4 in the voltammogram.



(37) (38)

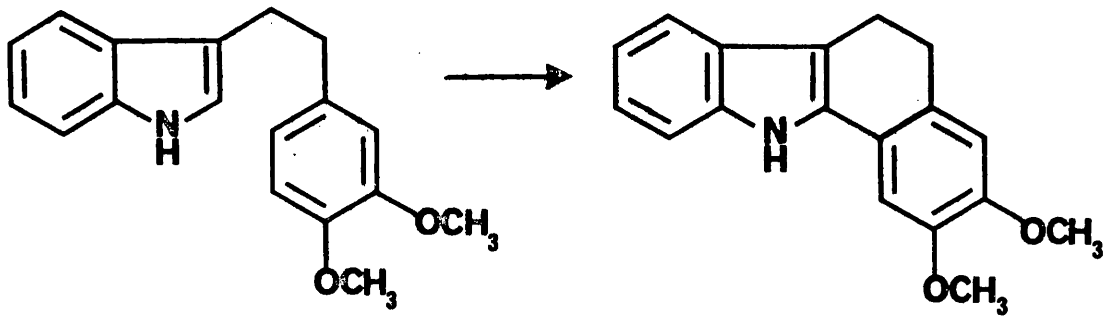
Ar = 3,4-dimethoxyphenyl

It was gratifying to note that the reduction potential of (38) is close to the reduction potential of the proposed 5, 6-dimethoxyoxindole imine cation (18) and we envisage the ultimate product in each case is a quinone.

<u>The synthesis and anodic oxidation of some indole substrates</u>

One of the first experiments carried out during this work was the attempted coupling of an indole nucleus to a veratryl unit, using 3-homoveratrylindole (39) as the substrate.

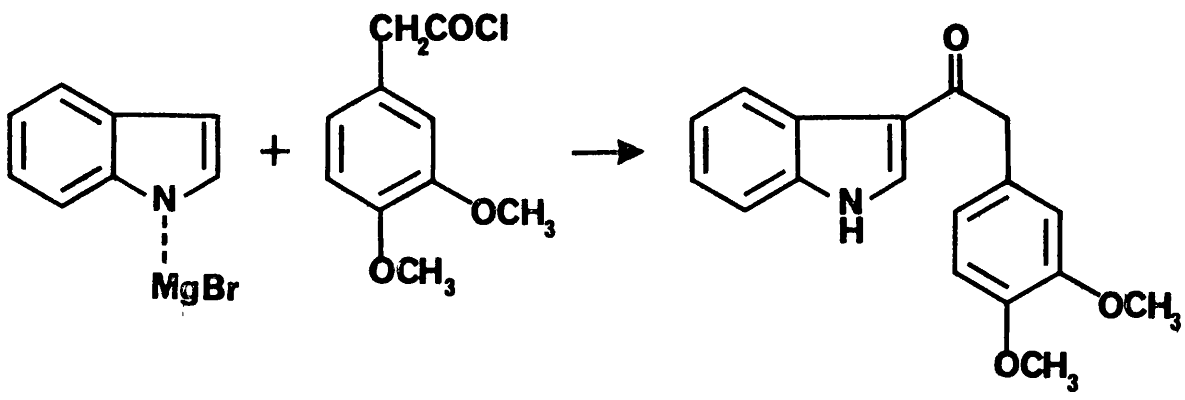
Of course, it is well known that indoles are unstable in oxidative conditions, but we envisaged that the presence



(39)

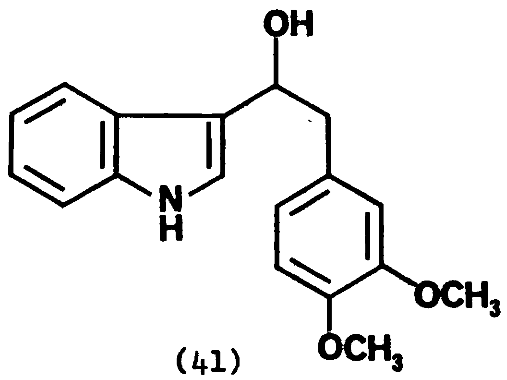
of an adjacent strongly nucleophilic nucleus might trap out the radical cation of the indole moiety and thus minimize the problems associated with uncontrolled intermolecular coupling.

The indole (39) was synthesised via a Grignard reaction: indole magnesium bromide was prepared by the addition of ethyl magnesium bromide to an equimolar amount of indole, the solution being homogenised with dichloromethane[35]. The indole magnesium bromide was then added to homoveratroyl chloride, the whole procedure was conducted at low temperature and on work-up , 3-homoveratroylindole (40) was obtained as a colourless powder (m.p. 174-176°).



(40)

The inverse addition of Grignard reagent was necessary to prevent two molecular equivalents of indole from adding to one mol. of the acid chloride[36]. Mass spectrometry of (40) showed the correct molecular ion m/e 295 and the infra-red spectrum showed absorptions at $3410cm^{-1}$ and $1630cm^{-1}$, the latter being consistent with the presence of a vinylogous amide. Reduction of the indole (40) with sodium borohydride in ethanol ($40-45^{o}$) and monitoring the reaction with ultra-violet spectroscopy resulted in the formation of a colourless compound (m.p. $149-150^{o}$) the mass spectrum of which showed a weak ion peak at m/e 297 (M^{+}). The infra-red spectrum showed the carbonyl absorption had disappeared with the formation of a large -OH peak at $3560cm^{-1}$. Confirmation that the alcohol (41) had been obtained was evident from the ^{1}H nmr spectrum which showed a deuterable (1H) singlet resonating at $\delta = 2.30$.



(41)

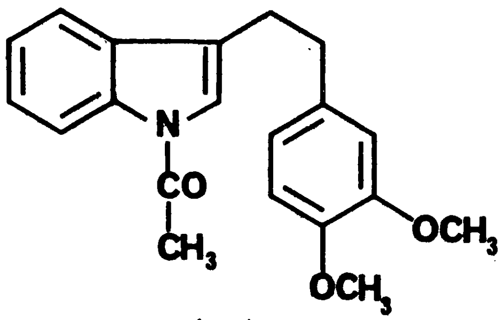
Reduction of the indole (40) in boiling ethanol gave a mixture of products, but complete reduction was effected in boiling n-propanol, which gave the indole (39) as a colourless solid (m.p. 114^{o}) the structure being corroborated by spectroscopic analysis.

The anodic oxidation of (39) in an acetonitrile-sodium perchlorate electrolyte proceeded at an electrode potential of 0.90v, but it was apparent from the outset that some electrode filming was occurring, pulsing techniques[37] failed to reduce polymer formation and the electrolysis was discontinued after 0.5F mol^{-1} of current had been consumed. During this short period the anolyte had turned bright fluorescent green and on work-up , the brown solid showed on T.L.C. analysis an unresolved trail, with no starting material discernable. From these results it seemed probable that (39) had undergone polymerization, possibly acid catalysed from the protons produced at the anode from the secondary chemical processes occurring after the initial electron transfer.

The cyclic voltammogram of the indole 39 (page 245) showed on the first cycle at 250 mV/sec anodic waves at 0.85v (O_1) and 1.01v (O_2) and a broad peak at 1.20v (O_3), with poorly defined cathodic peaks at 1.20v (R_3) and 0.86 (R_1) and 0.00v. We make no attempt to interpret this voltammogram, but it does show the indole unit is oxidized at a lower potential than the veratryl unit and it therefore is unlikely that direct oxidation of the latter occurred on the preparative experiment. A stable state voltammogram was unobtainable as electrode filming caused the gradual disappearance of all peaks.

In an attempt to raise the oxidation potential of the indole nucleus, (39) was acetylated to give N-acetyl-3-homoveratrylindole (42). Acetylation was effected by heating (39) in an acetic anhydride-acetic acid solution

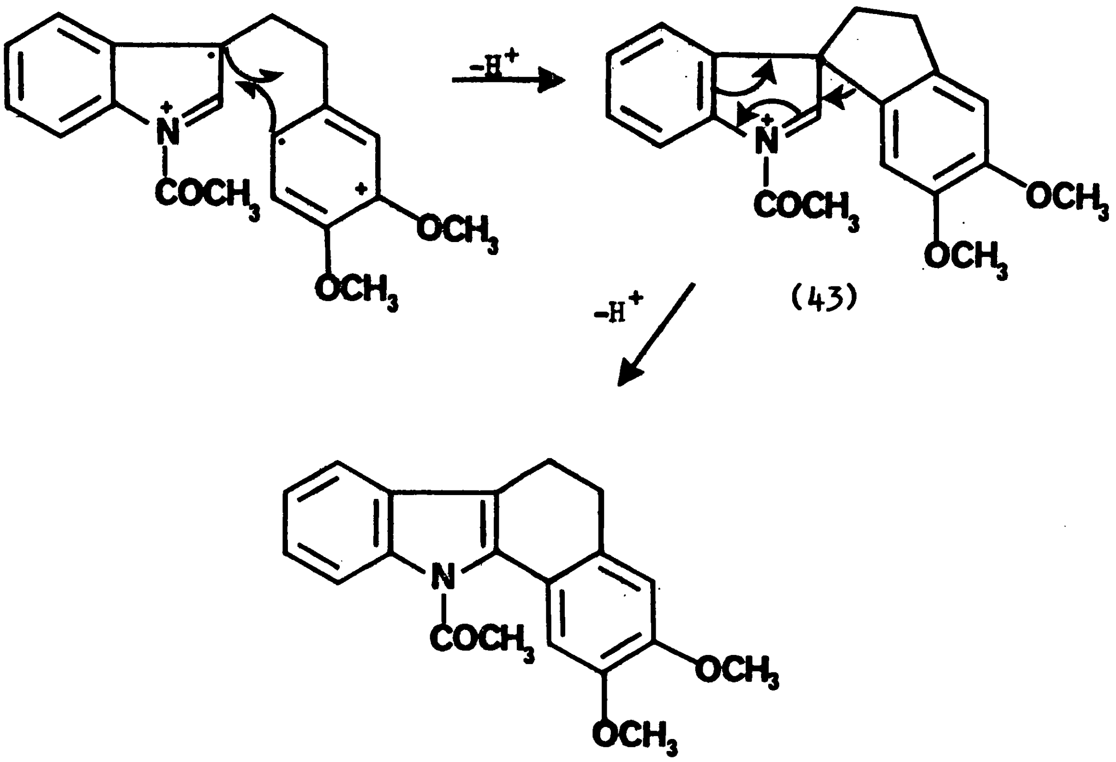
(9:1) for twelve hours to give (42) as a pale green powder (m.p. 108-110°).



(42)

The cyclic voltammogram of this compound (page 242) looked more promising, showing a single anodic peak at 1.05v (O_1) and a weak reduction peak (R_1) at 1.02v, indicated that a fast chemical reaction was occurring (cf. the small anodic peak at 0.80v is due to the presence of a little unacetylated indole). The preparative electrolysis of (42) was conducted at an electrode potential of 1.05v until 2F mol^{-1} of current had passed. Work-up of the dark red anolyte afforded a brown solid, but T.L.C. analysis showed a multitude of components. The major band from column chromatography (alumina, chloroform-pet. ether) proved to be a mixture of close running components but mass spectrometry of this crude product revealed major ion peaks in the m/e 590-600 region indicating these products were dimeric in nature, but further analysis of this product was unproductive.

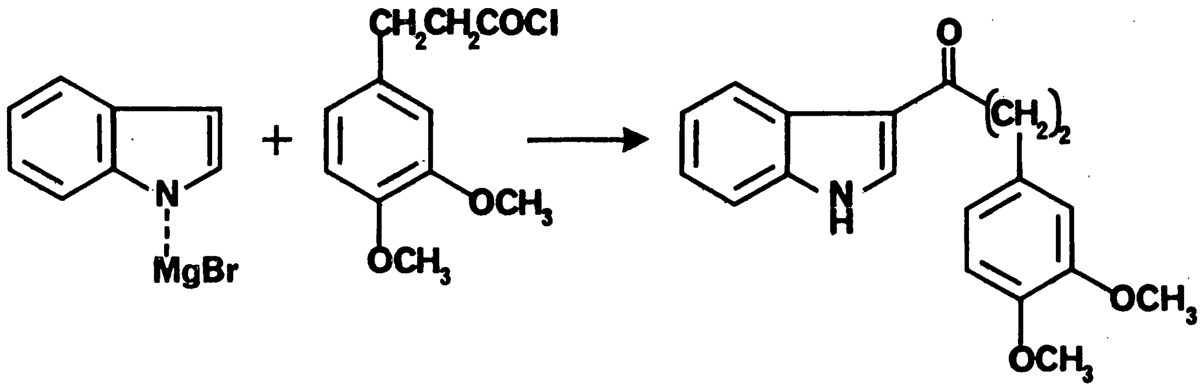
Indoles normally react at the 3-position and it is to be expected that the veratryl ring of (42) would couple to the 3-position initially and then rearrange to the 2-substituted indole.



(43)

The formation of the five membered alicycle in structure (43) might possibly be inhibitive on the grounds of ring strain and thus reduce the likelihood of intramolecular coupling although there are many examples of chemical cyclizations of a similar nature to be found in the literature. This contention could of course be surmounted by including an extra carbon atom in the side chain but then a seven membered product would result. This did seem an intriguing situation since compounds of the latter type are unknown and so we set about the synthesis and anodic oxidation of 3-β-(3, 4-dimethoxyphenyl)propionoyl indole (44). We deemed this a suitable substrate because not only did it possess a three carbon side chain, but the indole moiety was deactivated in the form of a vinylogous amide.

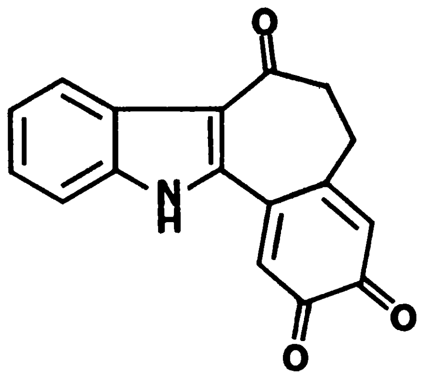
The synthesis of (44) followed a similar path to that of the indole (40), except β-(3, 4-dimethoxyphenyl)propionoyl chloride and indole magnesium bromide were used as the starting materials.



(44)

Work-up of the reaction afforded (44) as a colourless powder (m.p. 137-138°) the structure of which was confirmed by normal spectroscopic methods.

The anodic oxidation of (44) proceeded at an electrode potential of 1.25v, this voltage remaining steady until the passage of 2F mol^{-1} of current. During the electrolysis, the anolyte became black and a black "soot-like" deposit covered the anode. T.L.C. analysis of the product after work-up indicated some starting material was still present together with a dark red spot which proved to be light sensitive. Isolation of a dark red band from column chromatography (SiO_2, ethyl acetate-pet. ether) gave an evaporation of solvents and trituration in methanol a black powder (m.p. 220-240°, decomposing). Mass spectroscopic analysis at low ionizing potentials indicated ion peaks at m/e 279 and m/e 277 in a ratio of 3:1. The ^{1}H nmr spectrum (page 231) shows a broad (4H) singlet at $\delta = 2.95$ due to a $-CH_2-CH_2-$ linkage. Two (1H) singlets at $\delta = 6.56$ and $\delta = 6.80$ were ascribed to the two remaining protons of the veratryl ring which had obviously coupled through a position <u>para</u> to position 3 and four aromatic proton signals between $\delta = 7.25$ and $\delta = 8.02$ arise from the undisturbed 4, 5, 6 and 7 positions of the indole nucleus. No signal due to the indole 2-hydrogen was observed. The infra-red spectrum showed absorptions at $3340cm^{-1}$, $1670cm^{-1}$, $1658cm^{-1}$, $1644cm^{-1}$ and 1630^{-1} with a well resolved fingerprint region. The multiplicity of bands in the $1650cm^{-1}$ region indicated that both olefinic and carbonyl bonds were present in the structure, but most puzzeling feature of the ^1H nmr spectrum was the absence of signals due to methoxyl groups. The molecular ion was 32 m.u. lower than that of the starting material which would be consistent with the loss of two methyl groups from the veratryl moiety to form a quinone followed by coupling of this unit to the 2-position of the indole ring. We therefore propose the following structure.



m/e = 277

(45)

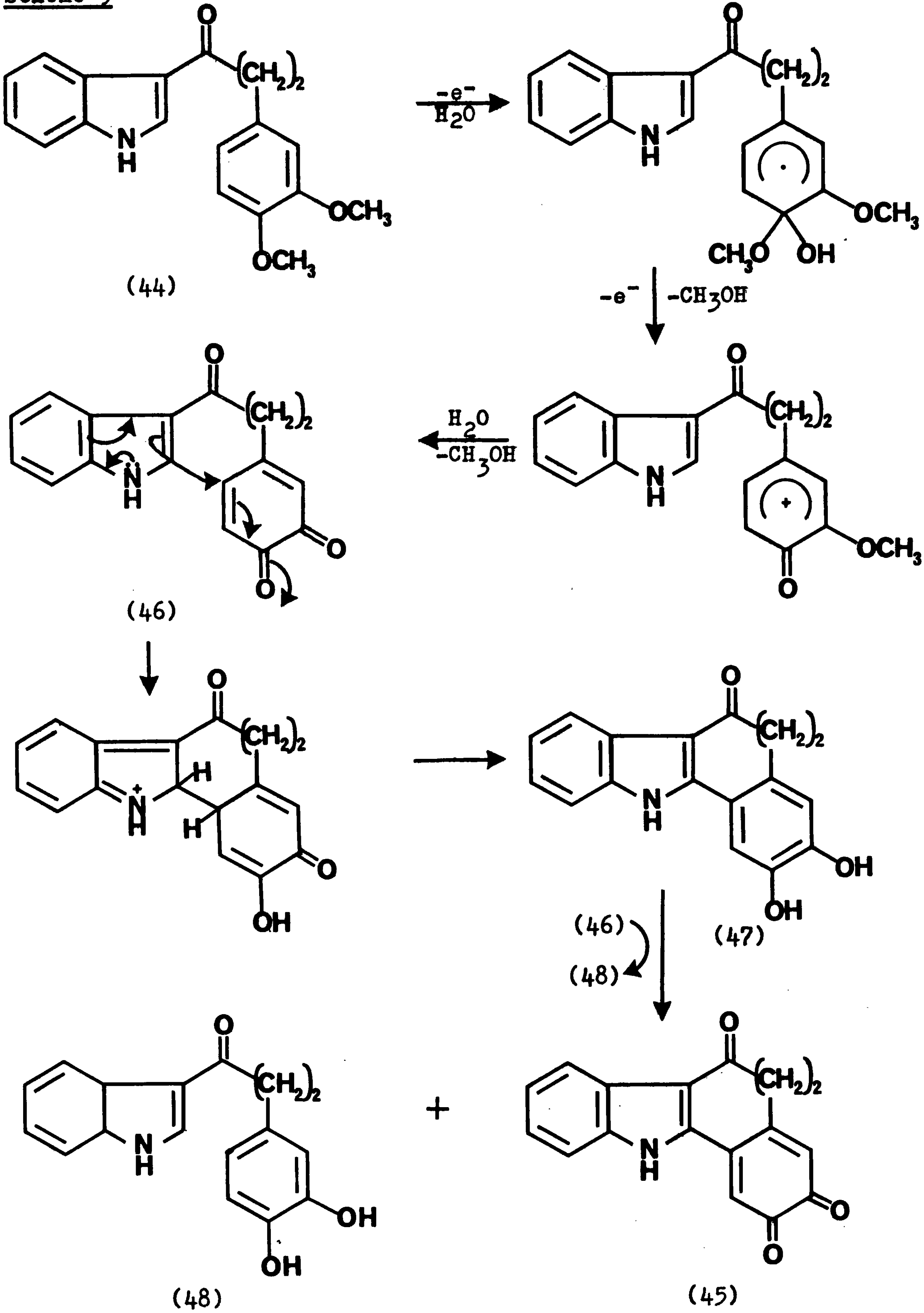
This is the first time to our knowledge that an indole ring has been electrochemically coupled to an adjacent aryl nucleus, and we propose that (45) is formed by the route shown in Scheme 9.

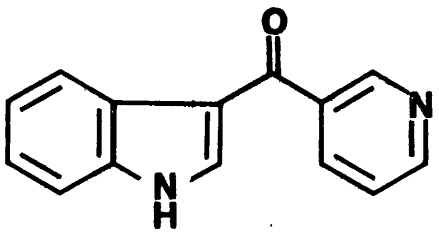
The proposal that the indole ring in not directly oxidized, but reacts in a nucleophilic sense with the ortho-quinone (46) is based mainly upon cyclic voltammetry evidence but there are some precedents for this in other electrochemical reactions[38,39]. We assume the transformation of the catechol (47) into the o-quinone product (45) may occur chemically in the presence of (46)[39], as the standard electrode potential (E_o) for the redox couple (46)-(48) will be greater than that for the couple (47)-(45)[40,41] although direct electrochemical oxidation is equally possible[42].

Cyclic voltammetry of the indole (44) at 250mV/sec (page 245) showed on the first cycle an anodic peak at 1.05v (O_1) and on the reverse scan a small cathodic peak was present at 1.04v (R_1). Quantitative measurement of peak current (using 1, 4-dimethoxybenzene as a standard[43]) indicated that at higher scan speeds (>750mV/sec) the peak (O_1) corresponds to the removal of just over one electron and hence is attributable to the veratryl ring. Evidence that the indole moiety is not oxidized at this potential was confirmed by the fact that no peaks below 1.50v were seen in the voltammogram of (49).

Potential scan cyclic voltammetry (P.S.C.V.) with a holding potential of 1.05v (ten seconds), gave on the first scan an additional small oxidative peak at 0.70v (O_2)

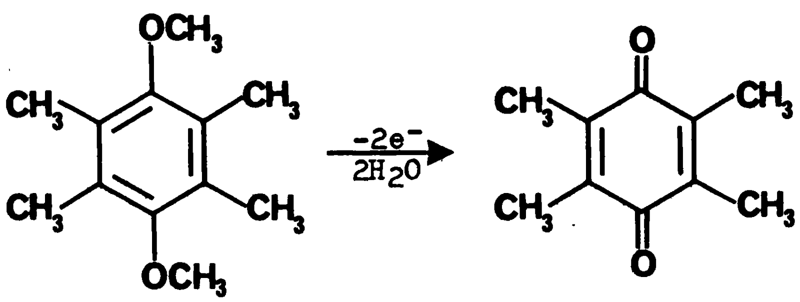
Scheme 9



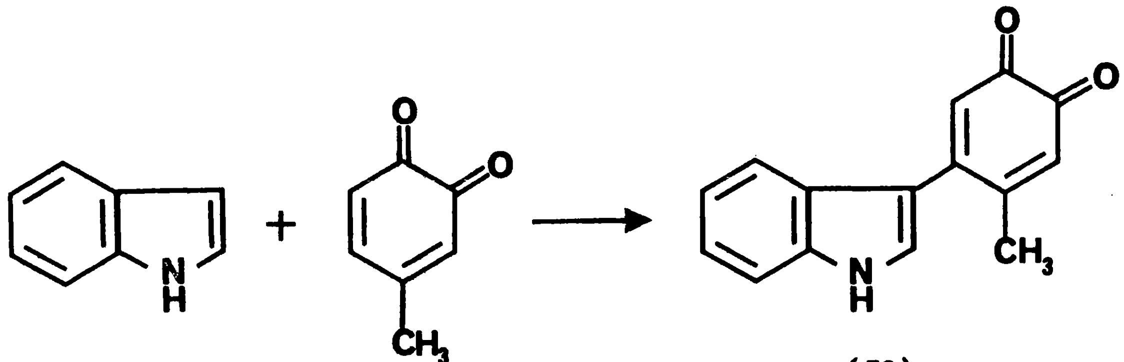


(49)

(page 245) which must be attributable to hydroxy-aryl intermediates, possibly (47) and (48). This is a typical anodic potential for quinone catechol systems[44], indeed formation of ortho-quinones from the anodic oxidation of methoxy phenols has been reported by Bruckenstein[42]. It seems that quinone formation is favoured when coupling reactions of alkoxy-aryl cation radicals are impeded (e.g. by steric hinderance) thus allowing more time for water to attack the charge species, for example, the anodic oxidation of dimethoxy-durene which undergoes a two electron oxidation to give duroquinone[45] at 1.28v.



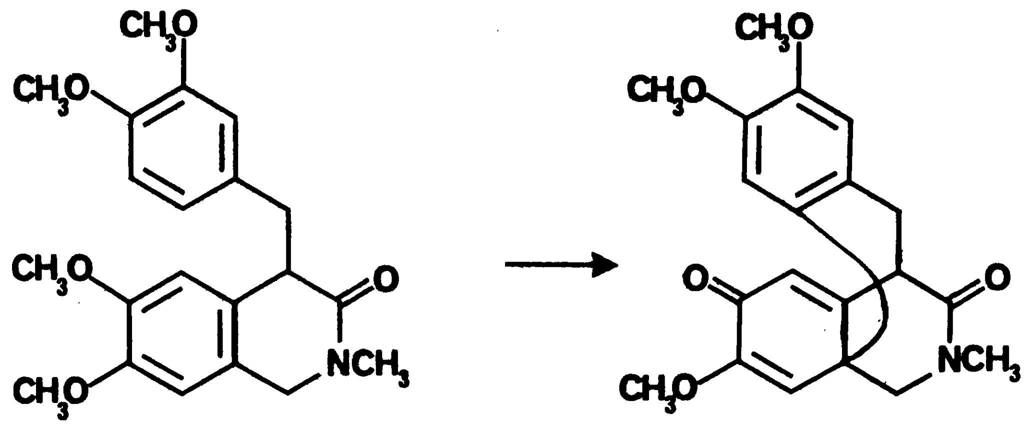
It is also known that indoles can yield Michael addition products with quinones, an example of particular relevance is the reaction of indole with 4-methyl-1,2-benzoquinone by Bu'lock[46], who reported that the 3-substituted indole (50) was formed.



(50)

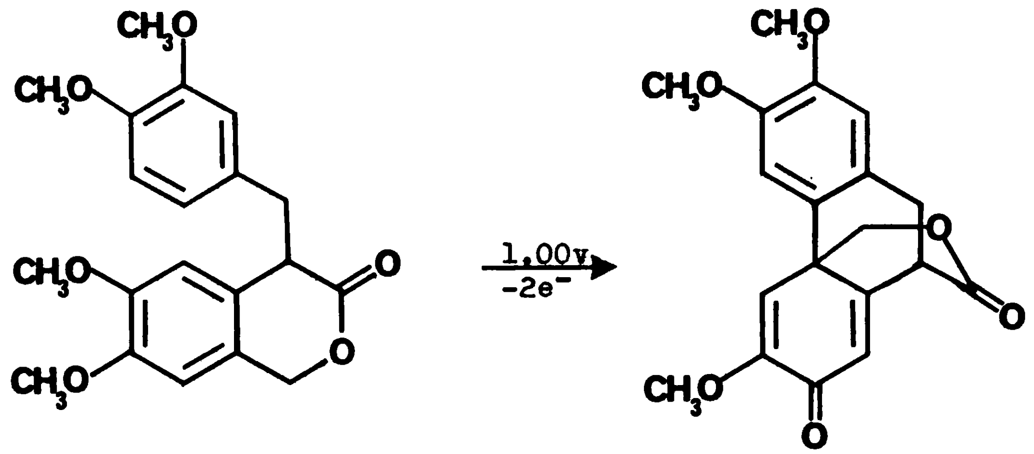
The only point of contention surrounding structure (45) is that mass spectroscopy of the sample shows a major ion peak at m/e 279; this probably attributable to a small amount of the more volatile catechol (47) which simply belies its true abundance. Clearly structure (45) is an interesting one, upon which more work should be done.

In the final series of experiments, attempts were made to synthesise 2-methyl-4-veratryl-6,7-dimethoxy-3-isoquinolone (51) in the hope that anodic oxidation would yield the dienone (52). Although considerable work has been carried out on isoquinoline based substrates due to the number of natural products based on this skeleton and the simplicity with which derivatives may be prepared, no electrochemical syntheses involving structures of type (51) have been reported. Special interest was expressed in this compound by Allen and Hanburys and we felt confident



(51) (52)

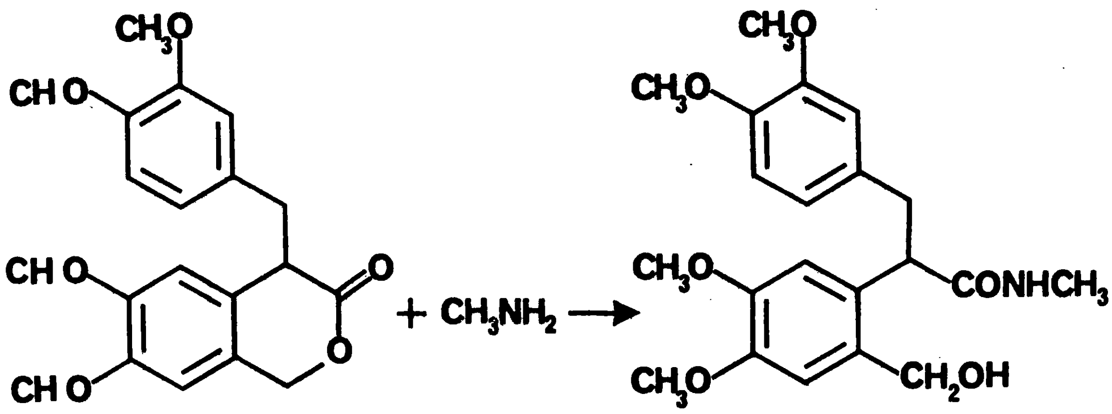
that (52) could be obtained, as the corresponding coumarin (53) has already been successfully cyclized to the dienone (54) in this laboratory[47].



(53) (54)

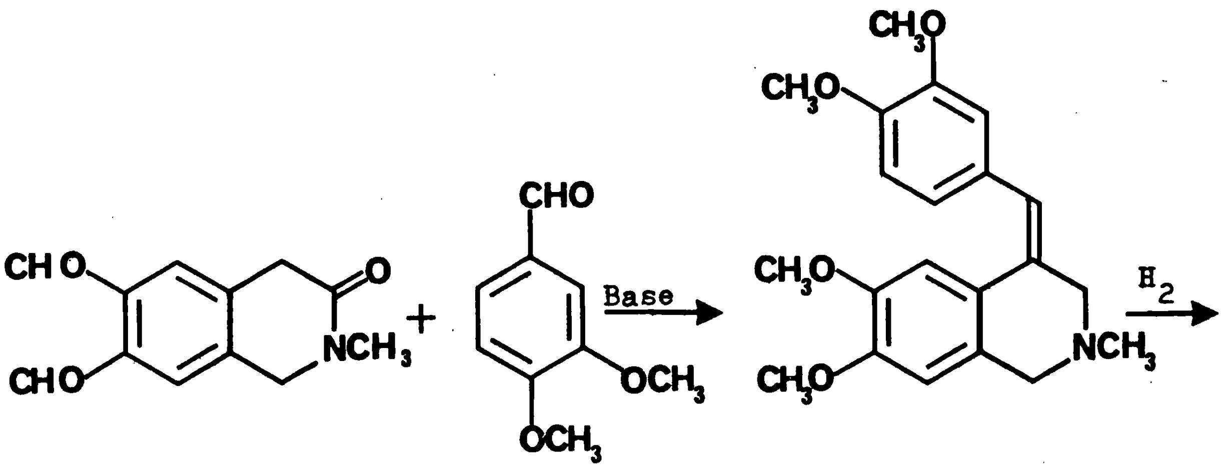
Several attempts to convert the coumarin (53) into the corresponding isoquinolone (51) with methylamine[48] resulted in failure, the only product obtained was the amide-alcohol (55) which not surprisingly was resistant to ring closure due to the stability of the amide function.

We speculated that the isoquinolone (51) could be prepared in a similar manner to the coumarin (53), namely



(53) (55)

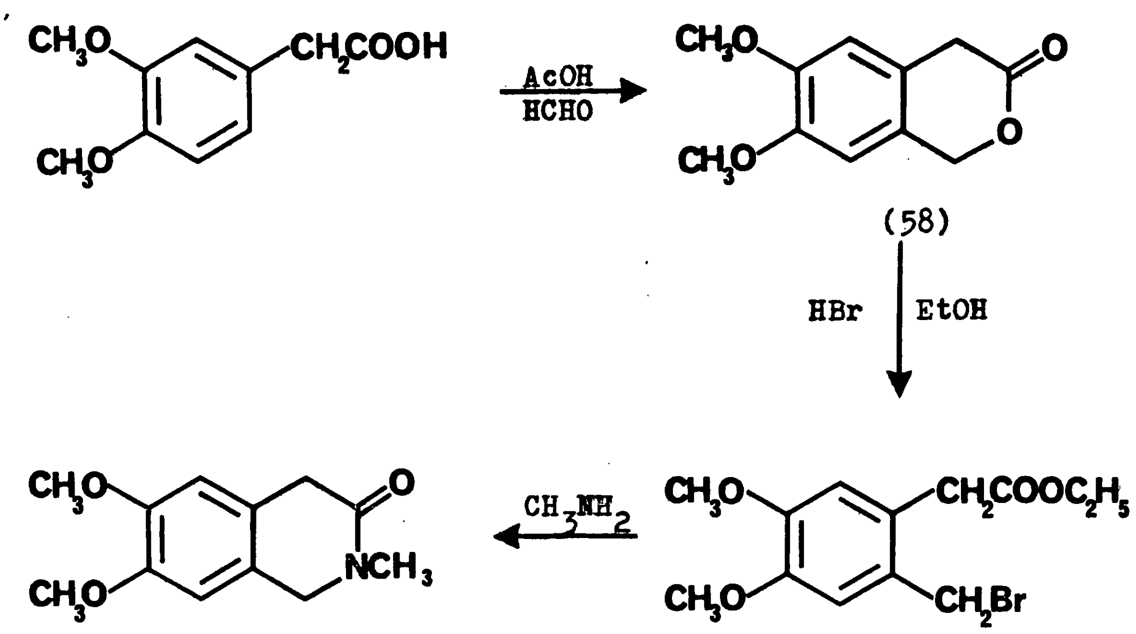
the condensation of veratraldehyde with 6, 7-dimethoxy-2-methyl-3-isoquinolone (56) in the presence of an organic base to give the 4-veratrylidene derivative (57) which could be catalytically reduced to (51).



(56) (57)

The synthesis of the quinolone (56) has been described by Finkelstein[49] who obtained it in a yield of 42% in a three step reaction, however, we found it necessary to alter considerably the experimental conditions to obtain adequate yields of product.

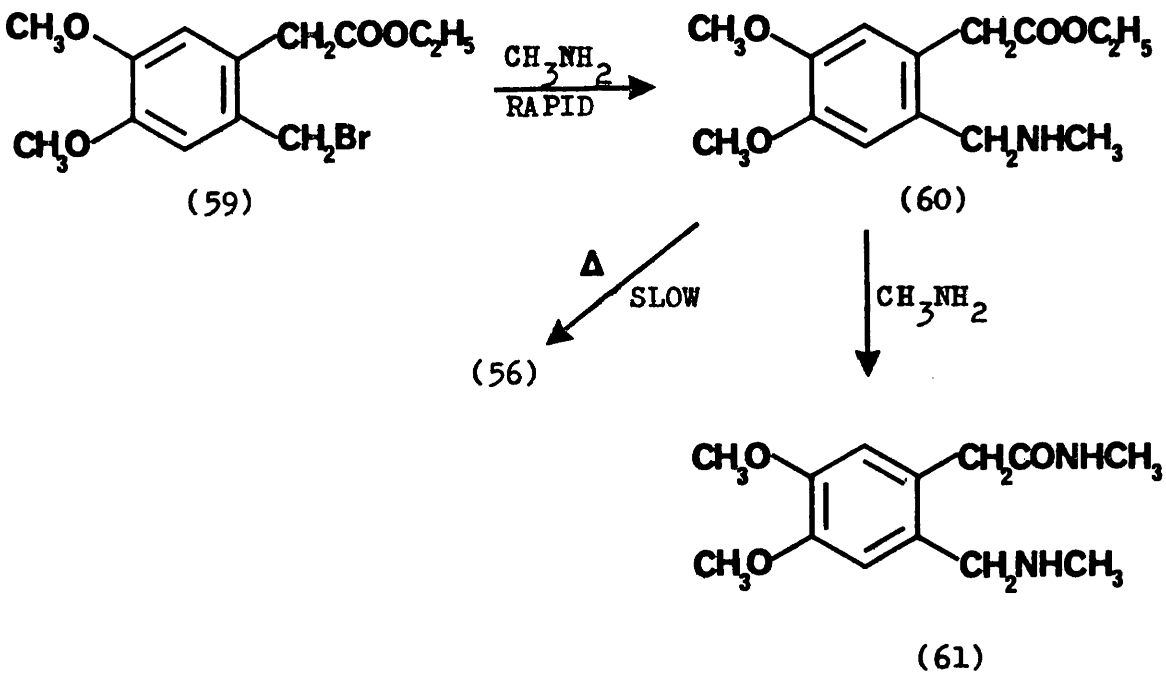
6, 7-Dimethoxy-3-isochromanone was obtained as a



(58)

(56) (59)

colourless solid (m.p. 108°)[49] and on standing in a solution of anydrous hydrobromic acid and ethanol for 24 hours, it gave the benzyl bromide (59) is a colourless oil, which slowly crystallized on standing (m.p. 55-57°). This compound proved to be unstable, but could be kept for several days if adequately cooled. Finkelstein dissolved the crude benzyl bromide in ethanolic methylamine solution and heated the mixture in an autoclave at 100°C for ten hours under 1000 psi of nitrogen. Unfortunately such equipment was not available for use and so modification of the last step was necessary. Compound (59) was dissolved in a solution of 33% methylamine in ethanol and ether (1:1) and heated in a stainless steel "bomb" for six hours at 100°C. On work-up a 17% yield of the isoquinolone (56) was obtained (m.p. 118-119°). Extension of the reaction time had little effect on the yield, and an examination of the mother liquors from the reaction by infra-red spectroscopy revealed broad absorptions at $3300cm^{-1}$, $3225cm^{-1}$, $1640cm^{-1}$ and $1605cm^{-1}$ (no starting material was present after six hours). Mass spectroscopic analysis of the crude product revealed a major ion peak at m/e 252 (M^+) which reinforced our opinion that the amide (61) was a major side product of this reaction, formed by the addition of two mol equivalents of methylamine to (59).



The reaction of methylamine with the benzyl bromide (59) to give (60) is apparently very fast as demonstrated by the immediate formation of a white precipitate on the addition of methylamine to an ethereal solution of (52). The cyclization of the resulting amine-ester (60) is much slower, requiring heat to speed the reaction, but in the presence of a large excess of methylamine a second mol of amine is free to add. Thus the reaction conditions were changed so that only a 2 mol. equivalents of methylamine were present, and the ethanolic solution was heated in a "bomb" at 100°C for two hours to give a 70% yield of (56).

Attempts to condense this isoquinolone (56) with veratraldehyde in the presence of an organic base under various conditions failed, T.L.C. analysis indicating that the starting materials remained unreacted. As the isochromanone (58) readily reacts with veratraldehyde under the same conditions we concluded that the acidity of the $-CH_2-$ function in the 4-position of the isoquinolone (56) is much reduced in comparison and is insufficient for an organic based catalysed condensation.

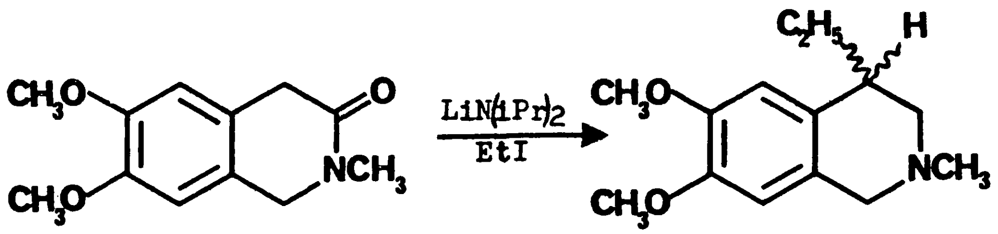
It is well known that amides can be alkylated at positions α to the carbonyl function[50] by the use of a suitably strong base and alkyl halide.

$$R-CH_2-\overset{\overset{\large O}{\|}}{C}-NR_2 \xrightarrow{\text{BASE}} R-\underset{-}{C}H-\overset{\overset{\large O}{\|}}{C}-NR_2 \xrightarrow{R^1X} R-\underset{\underset{\large R^1}{|}}{C}H-\overset{\overset{\large O}{\|}}{C}-NR_2$$

Lithium diisopropylamide is an exceptionally strong base and has been used by Creger for metalating carboxylic acids[51] where common reagents such as sodium hydride have failed. It is easily prepared by the reaction of equimolar quantities of butyl lithium and diisopropylamine in tetrahydrofuran.

$$n\ BuLi + (iPr)_2NH \xrightarrow{T.H.F.} Li^+\ N(iPr)_2^- + \text{Butane}$$

In order to estimate the effectiveness of this reagent with the isoquinolone (56), the latter was stirred for three hours with a 1.1M equivalent of lithium diisopropylamide in tetrahydrofuran. Addition of a 1 molar equivalent of ethyl iodide followed by stirring at room temperature for one hour gave on work-up a pale orange oil. The ^{1}H nmr spectrum (page 232) showed two sets of triplets ($\underline{J}$ = 9Hz) at δ= 0.62 and 0.80 (3H integral) with two octet signals at δ = 1.80 and δ = 2.15 (2H integral), arising from the two isomers of 2-methyl-4-ethyl-6,7-dimethoxy-3-isoquinolone (62). The infra-red spectrum confirmed this structure and showed an amide carbonyl absorption at 1640cm^{-1}.



(56) (62)

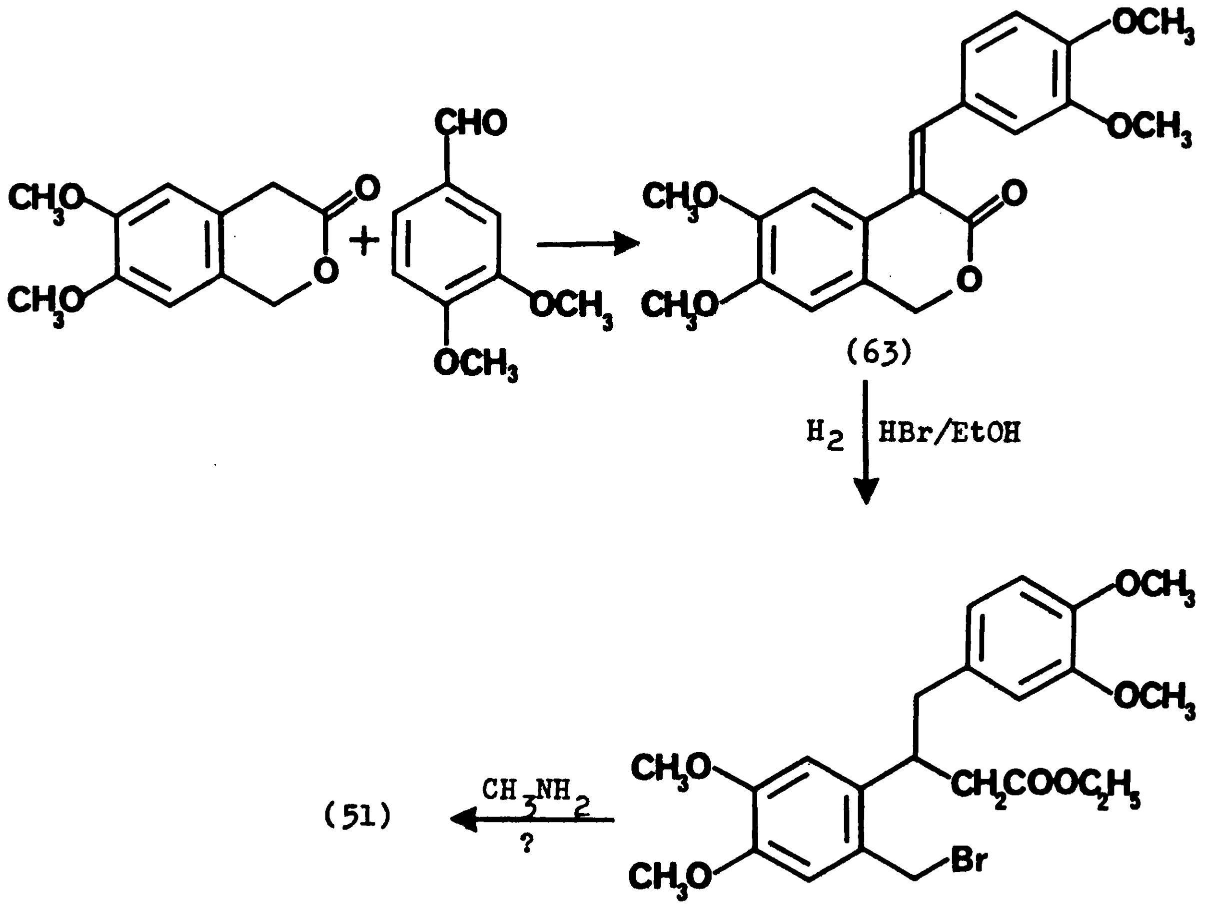
This therefore appeared to be a suitable method for the preparation of the 4-veratryl derivative (51) but later studies showed* that attempts to react the carbanion of (56) with veratryl chloride resulted in the formation of tricycloveratrylidene[33]. It seems that veratryl chloride is just as susceptible to trimerization in the presence of base as the benzyl chloride (34).

Although failure of the last step in this reaction sequence was disappointing, development of the route had not been in vain, for clearly the synthesis of the

* This last experiment was carried out by R Maskel.

isoquinolone (56) could be carried out with the veratryl group already in place.

The condensation of equimolar quantities of veratraldehyde and 6, 7-dimethoxy-3-isochromanone (58) gave the 4-veratrylidene derivative (73) as a pale yellow powder (m.p. 176°)[48]. Catalytic hydrogenation gave on work-up 4-veratryl-6, 7-dimethoxy-3-isochromanone (m.p. 106°)[48] and this on standing in anhydrous hydrobromic acid and ethanol gave a colourless oil which slowly crystallized (7 days) to give a colourless solid (m.p. 84°).



(63)

(51)

(64)

The ^{1}H nmr spectrum confirmed the presence of an ethyl group, with a (3H) triplet (J = 6Hz) at δ = 1.10 and a (2H) quartet at δ = 4.01. Mass spectroscopy revealed two molecular ion peaks at m/e 468 (M^+) and m/e 466 (M^+) characteristic of a molecule containing one bromine atom and the infra-red spectrum showed an ester carbonyl absorption at 1725cm^{-1}: all this data being consistent for the benzyl bromide (64).

Unfortunately due to lack of time, we have not yet attempted the last stage in this synthesis, namely the reaction of methylamine with (64) but we feel confident that this is the method of choice for the synthesis of (51).

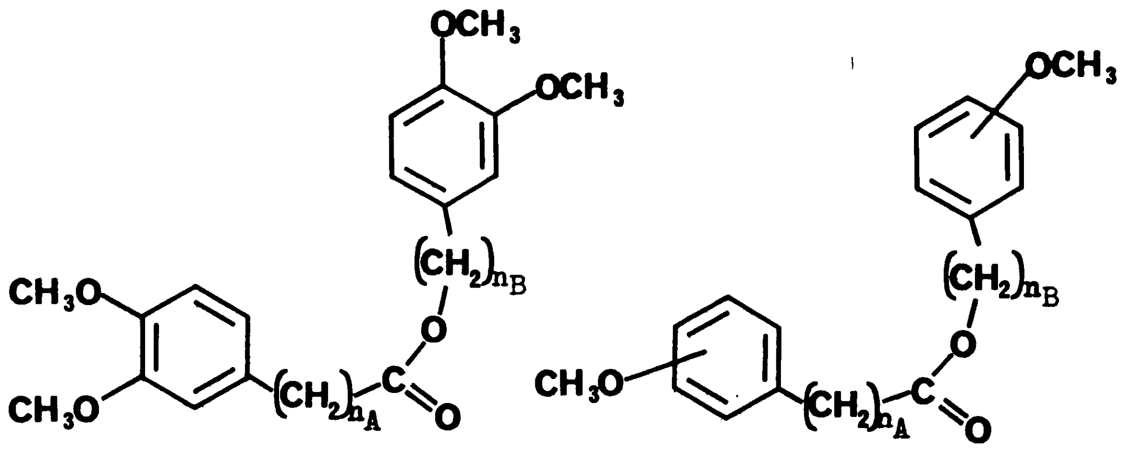
Cyclic voltammetric measurements on the isoquinolone (56) reveal that it is oxidised at a potential (1.00V) close to that of a veratryl ring and therefore the anodic oxidation of (51) is highly likely to result in the formation of the dienone (52).

CHAPTER 3

The Anodic Oxidation of some simple Diaryl Esters

In parallel with our experiments on diaryl alkyl amides a study was made of the analogous esters. Here we anticipated similar results, but should intramolecular cyclization occur, then the rather more easy hydrolytic cleavage of an ester function would open the way to further synthetic opportunities.

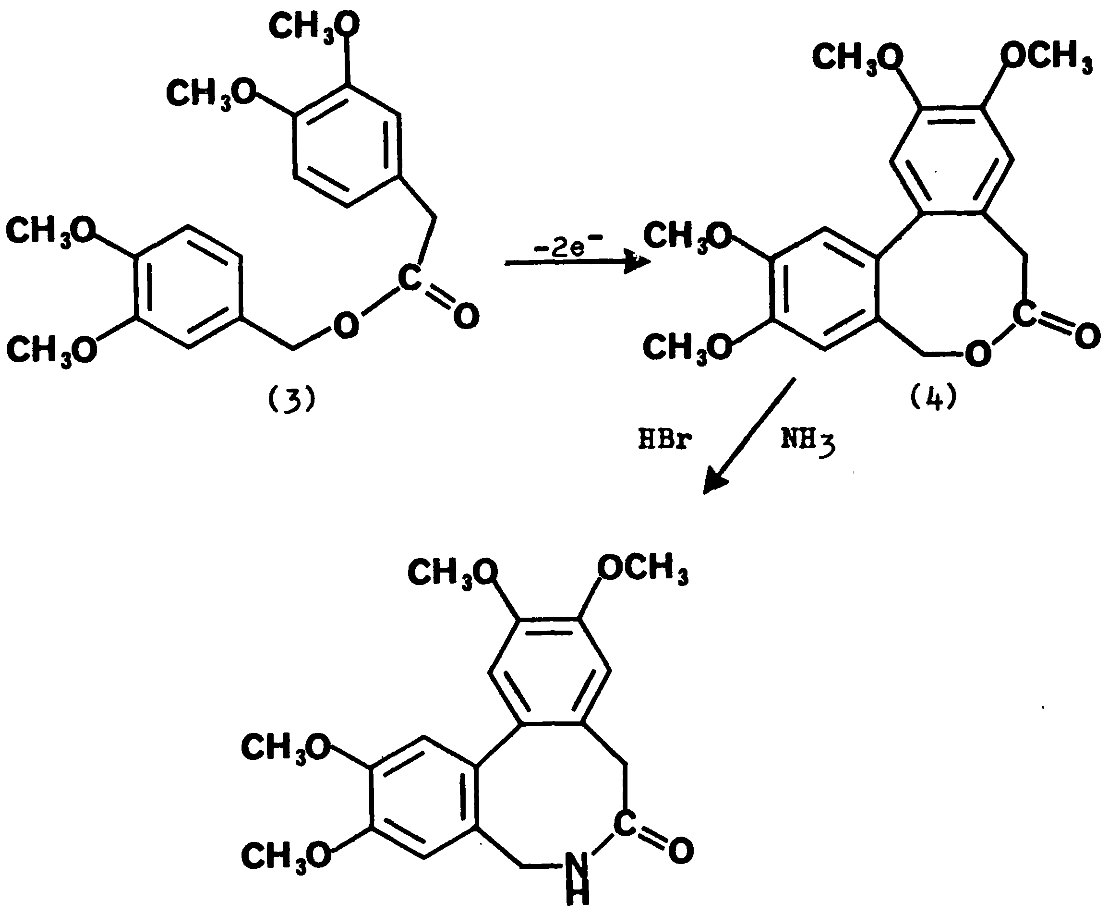
Once again little reference could be found in the chemical literature to the electrochemical oxidation of esters, apart from Miller's work on simple aryl derivatives[1] and some observations from this laboratory[2]. In this new study, we chose to examine mono- and dimethoxylated aryl esters of the general formulae (1) and (2).



(1) (2)

Our first objective was the preparation and oxidation of the ester (3). It will be recalled that in the case of the corresponding amide (page 51) we encountered adverse stereochemical effects which precluded intramolecular cyclization. These effects are a direct result of the double bond character of the C-N function, but in esters this problem is not so pronounced. While it is known that simple esters prefer a <u>trans</u> conformation of bulky groups

(E form)[3,4]; a moderate degree of rotatory oscillation about the ester linkage occurs[5]. Thus we felt that there was a much better chance of intramolecular coupling in (3) and it might also be possible to convert the expected product (4) into the desired nitrogen heterocycle (5) by standard methods:

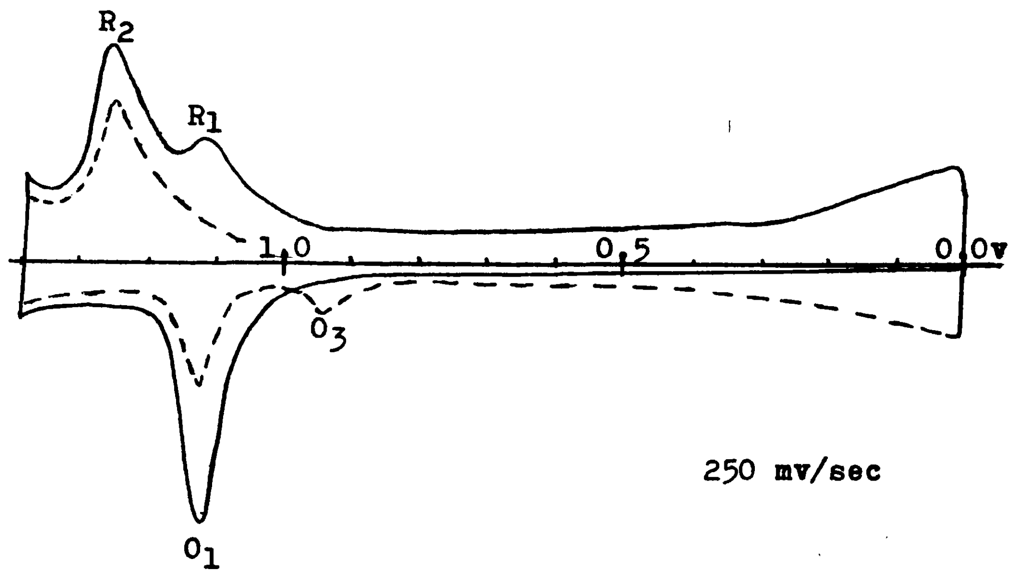


(3) (4) (5)

The ester (3) was prepared from veratryl alcohol and homoveratroyl chloride and oxidised at an initial anode potential of 1.15v (vs SCE) in acetonitrile/sodium perchlorate electrolyte. The colour of the anolyte became dark purple and the experiment was continued until 2F mol^{-1} of current had been consumed. Some electrode filming was noted and work-up gave only a dark coloured amorphous solid which appeared to be a salt. Little could be done to purify this intractable material and next we turned to an analysis of the cyclic voltammogram of the starting material in order that we might explain the unproductiveness of the electrolysis.

This voltammogram (figure 1) shows an initial anodic peak at 1.12v (O_1) with a large reductive wave at 1.24v (R_2) and a smaller reductive peak at 1.11v (R_1). The steady state trace, obtained after 20 scans, (dotted line figure 1) shows a new anodic peak at 0.95v (O_3), but R_1 has now disappeared.

Figure 1



One surprising feature of the steady state trace is that R_2 has no oxidative counterpart: we may assume, however, that this wave arises from the reduction of an oxidised product which forms after the first electron transfer process at O_1. If the chemical product is formed sufficiently slowly and is rapidly oxidised at about the same potential, then no new clearly defined anodic peak will be observed; simply a higher background current above O_1. We may then surmise the events at the electrode in the following way:

$$A \underset{(1)}{\overset{-ne^-(O_1)}{\rightleftharpoons}} [A]^{n+} \xrightarrow[\text{reaction}]{\text{slow chemical}} B + nH^+ \xrightarrow[-n'e^-]{\text{fast}} [B]^{n'+}$$

$$\text{(2)} \qquad \text{(3)}$$

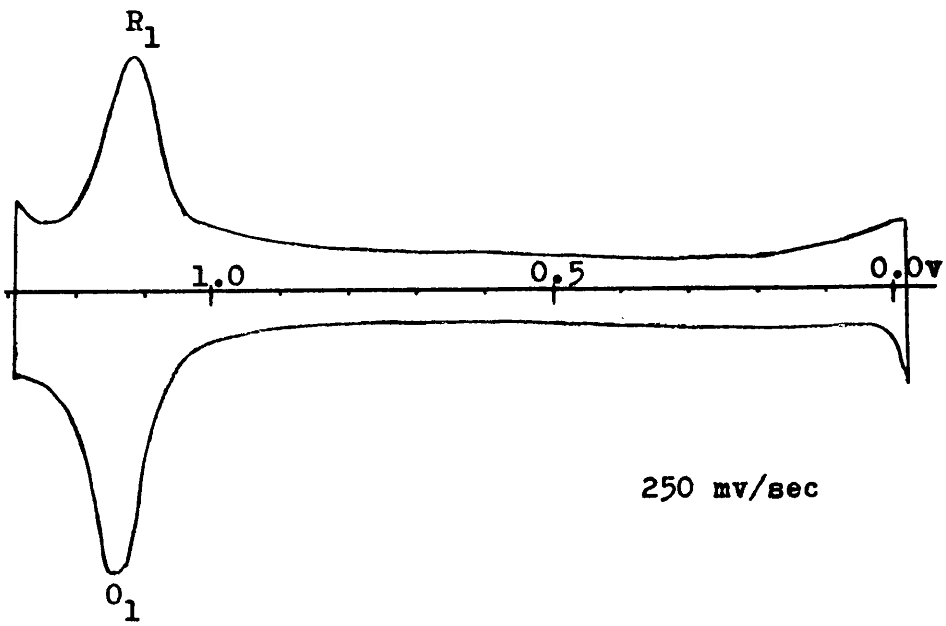
$$[B]^{n'+} \xrightarrow[(4)]{+\,n'e\ (R_2)} B$$

A = substrate

B = chemical product

Once reformed (step 4), the chemical product B seemed to undergo a chemical reaction to refurbish A, since a cyclic voltammogram (figure 2) using a rotating platinum electrode (R.P.E.) showed a simple redox couple at 1.15v (O_1)–1.12v (R_1), with no evidence of chemical products.

Figure 2

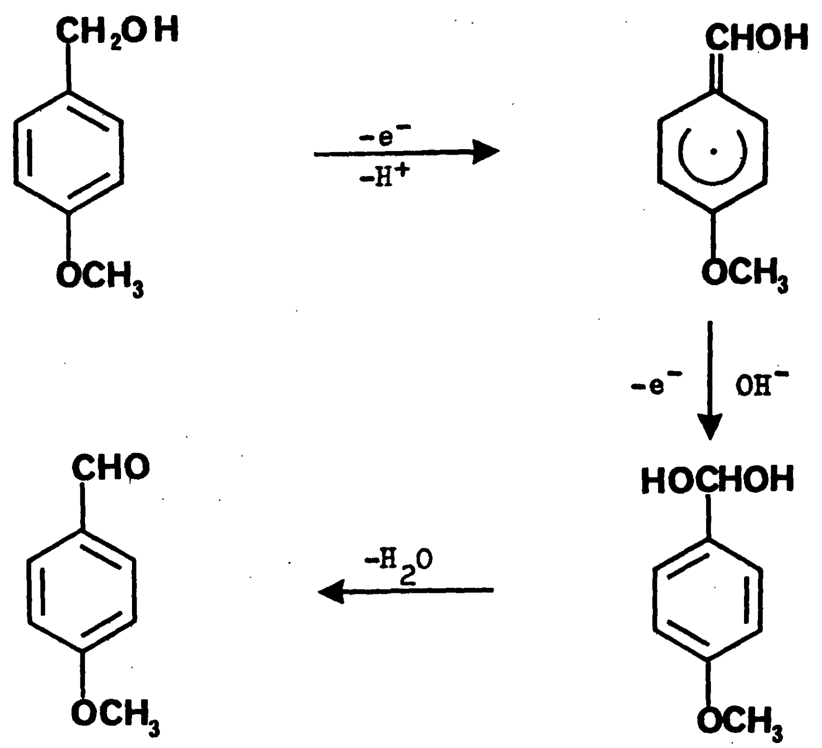


The ratio O_1/R_1 in this last trace is approximately 1 and we assume that these two peaks are due to the removal of two electrons from the ester (3) to form the corresponding diradical dication which is then reduced back again. Rapid coupling followed by further electron transfer can be ruled out because the ratio O_1/R_1 would now be greater than unity.

These results are puzzeling and it became necessary to consider what other changes might be occurring during electrolysis.

It is well known that benzyl alcohols are oxidized electrochemically to the corresponding benzaldehydes. Lund[6] has reported the anodic conversion of p-methoxybenzylalcohol to p-anisaldehyde in the same electrolyte system as that employed by us for the oxidation of the ester (3). He suggests that the mechanism of the reaction is as shown below in Scheme 1.

Scheme 1



This behaviour is not restricted to alcohols, indeed both related ethers[1,7] and esters[1] yield aldehydes. The benzylic methylene function is the key, and it appears that the critical factor in determining whether oxidation will occur is the ease with which the first proton is lost from the radical cation. In turn this depends upon:

(a) the latent acidity of the benzylic protons,

(b) the stability of the radical cation,

(c) the electronic configuration of the substrate.

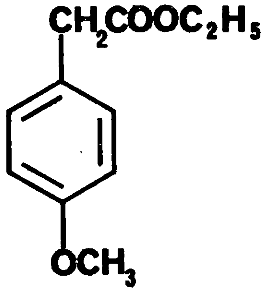
Incidentally, in nearly all cases where benzylic oxidation occurs electrode filming has been a major problem[1,6,8,9] although the nature of the insulating material has never been established.

^{1}H nmr spectroscopy provides a rapid, if approximate, guide to latent acidity and table 1 indicates the chemical shift positions (relative to internal TMS), of the benzylic methylene proton resonances of several compounds.

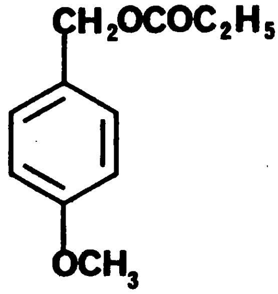
Table 1

	Compound	Chemical Shift (δ ppm)
(a)	Ph-CH_2-OH	4.44
(b)	Ph-CH_2-O-CO	4.62
(c)	Ph-CH_2-NH-CO	4.30
(d)	Ph-CH_2-CO-O-	3.40
(e)	Ph-CH_2-CO-NH	2.67

The δ values for alcohols (a) and the esters (b) are not very different (·22 Hz) from those of the amides (c) and thus it is probable that the filming problems discussed in the first chapter are attributable to the similar effects resulting from benzylic oxidation. The chemical shift position of the methylene group in the ester (d) indicates lower latent acidity and thus proton loss should be slower. In order to test this postulate, quantitative cyclic voltammetric measurements were conducted on the two simple esters (6) and (7).



(6)



(7)

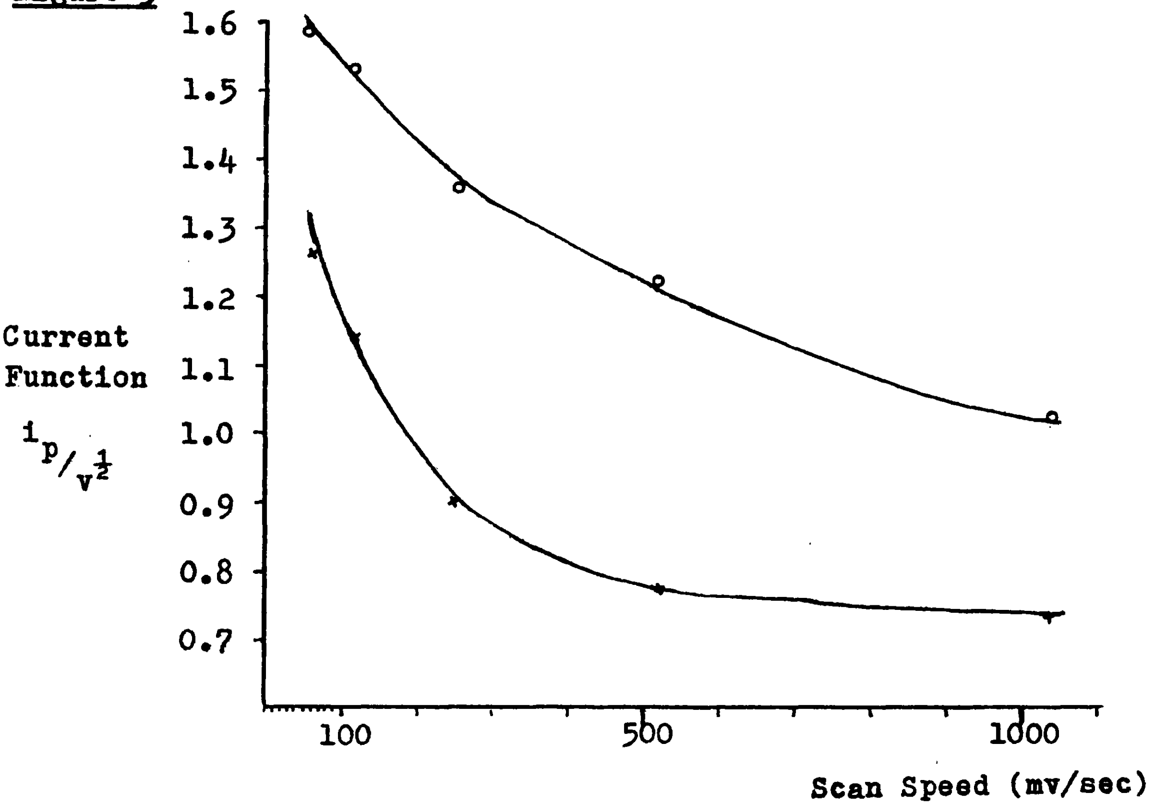
The results of peak current measurements versus scan speeds for equimolar solutions (10^{-3}) are compared and tabulated (Table 2) and also displayed graphically (figure 3).

Table 2

	Ester 6			Ester 7		
Scan Speed	ip	Ep	$ip/v^{1}/_{2}$	ip	Ep	$ip/v^{1}/_{2}$
60 mV/sec	9.8	1.30v	1.27	12.3	1.29	1.59
120 mV/sec	12.6	1.32v	1.14	16.8	1.30	1.53
260 mV/sec	14.5	1.35v	0.90	22.0	1.30	1.37
520 mV/sec	17.8	1.39v	0.78	28.0	1.31	1.23
1080 mV/sec	24.9	1.43v	0.75	34.0	1.33	1.03

For all scan speeds the peak current ip for ethyl 4-methoxyphenylacetate (6) was less than that of 4-methoxybenzylpropionate (7). Moreover, at 260 mV/sec the peak current for the latter compound was almost twice that of 1, 4-methoxybenzene.

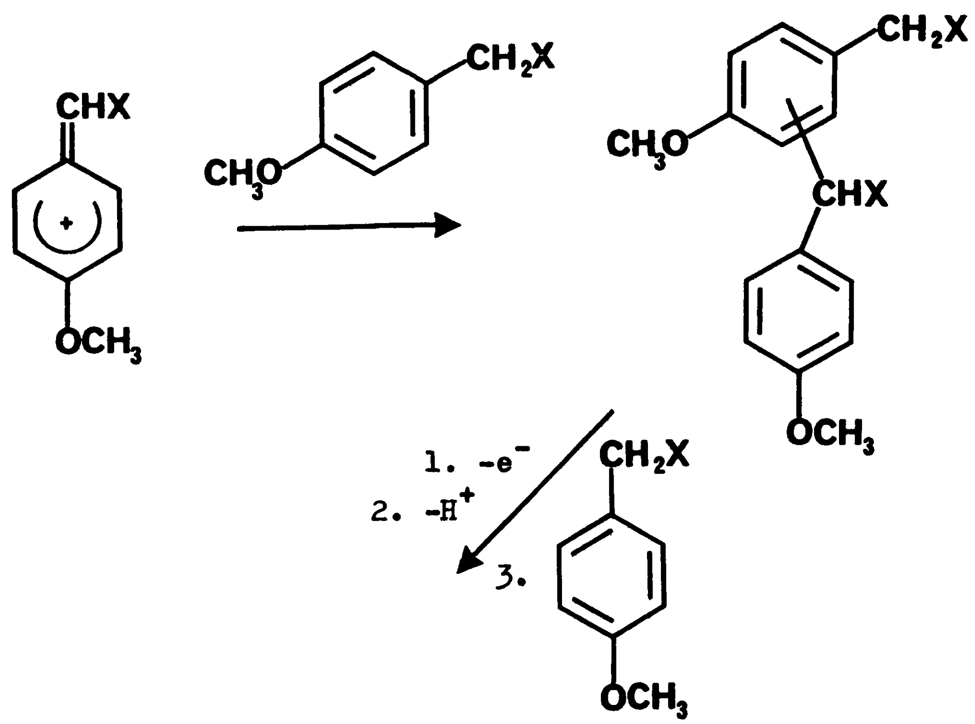
Figure 3



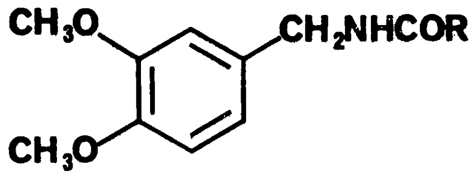
Together, these observations suggest that in this scan range 4-methoxybenzylpropionate (7) undergoes a fast ECE reaction. Further evidence in favour of this view rests on the fact that both peak potentials and peak widths increase with increasing scan speed[10]. An interesting comparison can be made here between the behaviour of (7) and dibenzyl ether. The last compound is known to undergo facile oxidation[7].

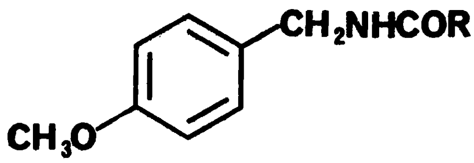
Similar measurements on veratryl alcohol indicate that only 1.3e mol^{-1} are transferred at the slowest scan speed (60 mV/sec). This imprecise result may be expected since the dimethoxylated ring system imparts more stability to the corresponding radical cation than does the monomethoxylated nucleus of either (6) or (7). Additionally, of course, the veratryl derivative has a free para (to OMe) position so that intermolecular coupling is favoured. In this way some positive charge could be discharged, although benzylic oxidation may not be ruled out completely.

We believe that a combination of adverse stereochemical factors and the presence of an "acidic" benzylic methylene function are responsible for electrode filming, thus when rapid intramolecular coupling is precluded oxidation at the benzylic position becomes a major reaction and under certain circumstances leads on to polymer formation. As mentioned earlier the nature of anode films has not been resolved, but it is possible to speculate that, if in the Lund mechanism (Scheme 1) the substrate acts as its own nucleophile, intermolecularly coupled products can easily form which could then oxidise and perpetuate a chain reaction:



The intractable nature of the films that we have encountered do not allow us to provide evidence in support of such a sequence, but we note that, apart from one exception, all the amides discussed in Chapter 1 which caused filming contained the following sub structures:





Interestingly, the oxidation of monomethoxylated amides (for example 26, page 9) resulted in more rapid electrode insulation than was the case for their dimethoxylated counterparts, and in one example of the latter type (6, page 51) electrode filming problems were surmounted.

To ascertain that the benzylic oxidation of simple amides results in similar products to, say, dibenzyl ether[7], we examined an "uncontrolled" anodic potential electrolysis of N, N-dibenzylacetamide (8); here, since the ring is not activated by methoxylation, the compound's nucleophilicity is low.

The preparative electrolysis in acetonitrile/sodium perchlorate commenced at an anode potential of 1.90v, but rapidly rose in the course of seconds to 2.30v. This potential was maintained until all the substrate had been consumed (2F mol^{-1}). T.L.C. analysis indicated a multicomponent product which was subjected to column chromatography on silica gel ($CHCl_3$: EtOH 9:1). The combined early fractions were then analysed by G.L.C. using two column systems, OV1 and apiezon L, comparisons of retention times were then made with a wide variety of likely test compounds, the choice of which was aided by mass spectrometric measurements upon the mixture. The results are shown in Table 3 and 4.

Table 3 (OV1) $t = 137^o$ $f = 60\ cm^3/min$

Retention time	Intensity	Corresponds to:
22 sec	weak	Benzyl alcohol
26 sec	strong	Benzaldehyde, o and p cresols
1 min - 10 sec	medium	Benzoic acid
1 min - 40 sec	weak	unknown
9 min - 40 sec	medium	unknown
33 min	very strong	starting material

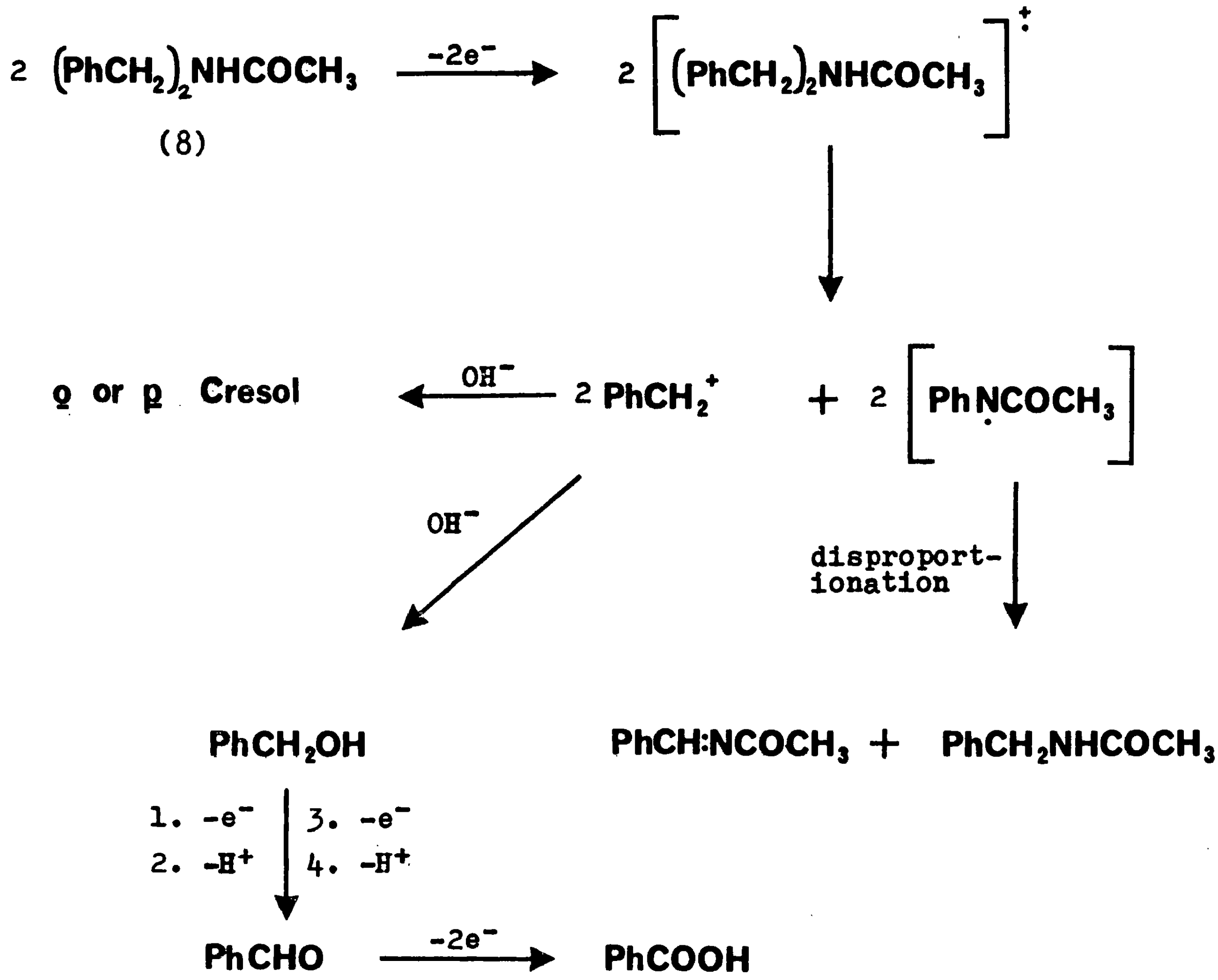
Table 4 Apeazon L $t = 100^oC$ $f = 50\ cm^3/min$

Retention time	Intensity	Corresponds to:
1 min - 45 sec	weak	unknown
2 min - 35 sec	strong	Benzaldehyde
3 min - 30 sec	weak	Benzyl alcohol
4 min - 5 sec	weak	o or p cresol
5 min - 2 sec	medium	unknown
6 min	weak	Benzoic acid

(N.B. the presence of N-benzylacetamide was not checked).

Further evidence that benzoic acid and o and p cresols were present was provided by their physical isolation from the basic washings of the initial electrolysis product.

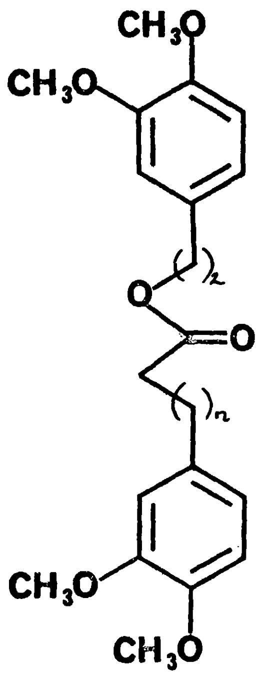
It is clear then that amides bearing benzylic methylene groups may undergo this general type of oxidation and we are able to account for the products obtained from the amide (8) by the following reaction scheme.



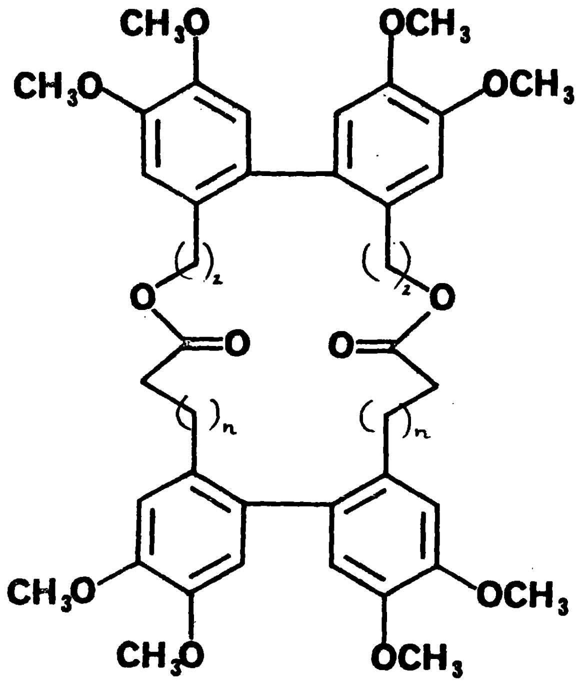
The above mechanism is based upon that proposed by Utley for the anodic oxidation of bibenzyl ether[7], but we envisage this type of process is also applicable to the amide (8).

Should benzylic oxidation contribute to filming in in the case of the ester (3) and the formation of a resinous product, then it would be instructive to examine the homologue (9), where the additional methylene group is interposed between the oxygen atom of the ester function and the benzylic unit.

The oxidation of this compound was conducted at an anode potential of 1.10v until 2F mol^{-1} of current had been consumed.



(9) n= o

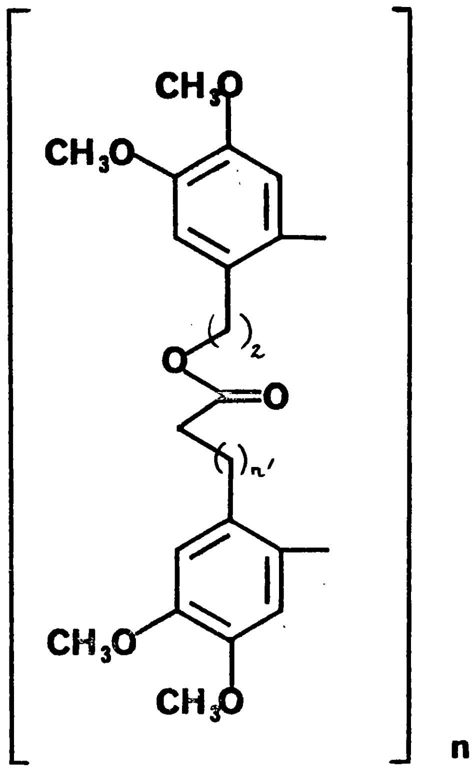


(10) n= o

No filming was noted, and on work-up an orange coloured oily product was obtained. T.L.C. analysis showed several poorly resolved components and column chromatography eventually afforded two pale orange amorphous solids.

Mass spectrometry revealed that one of these was probably a "dimer" of (9) and the ^{1}H nmr spectrum supports this view showing that the point of linkage is through the aryl nuclei, moreover, only four aromatic signals are observed. We propose structure (10) for this compound since "large ring" structures of this type have been reported by Parker[11] as the oxidative products of related diarylalkanes.

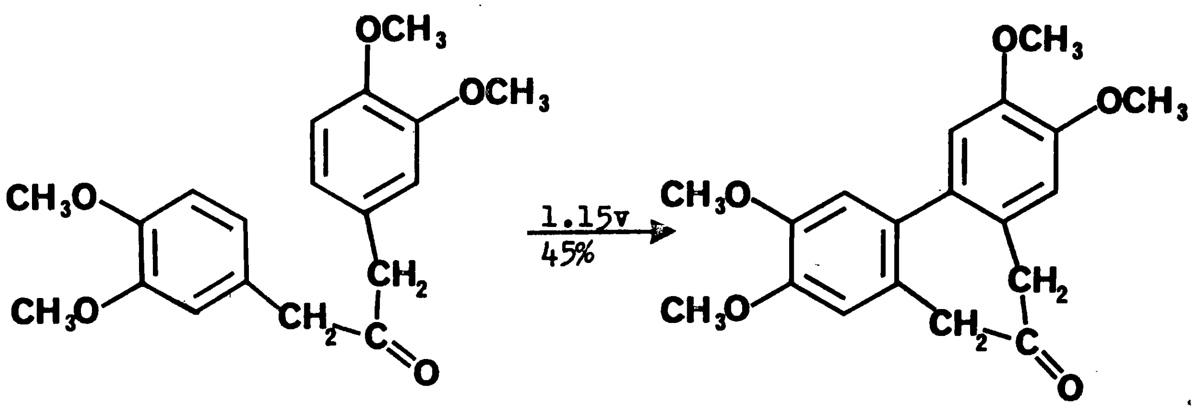
The second substance had molecular ion peaks at m/e 720 and 1080 (and probably higher mass ions as well), and since the ^{1}H nmr spectrum agains reveals four aromatic resonances, we propose that "dimeric" and "trimeric" species are present, probably of the form (11) where n = 2 or 3.



(11) $n' = 0$

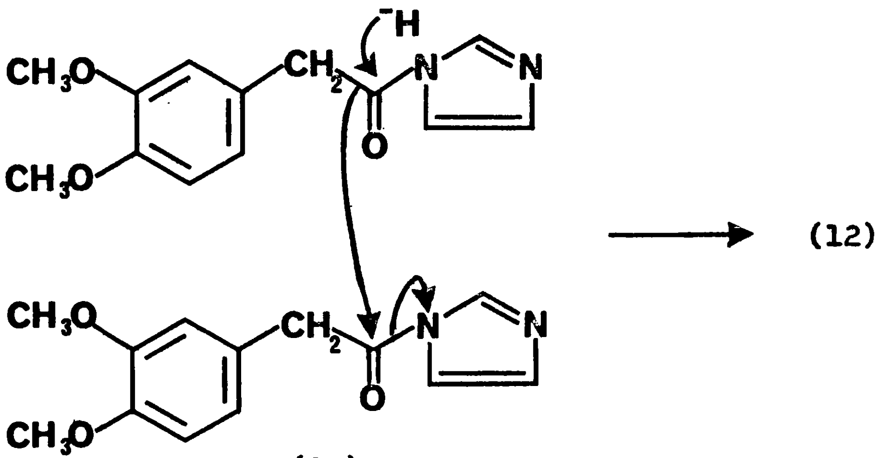
In some of these observations it seems that anodic oxidation of substrates bearing an Ar-CH_2-O- unit (Ar is a methoxylated ring) will invariably be unproductive, but an Ar-CH_2-CO system may be employed.

In previous work unrelated to this topic, bis 1, 3-(3, 4-dimethoxyphenyl)-2-propanone (12) had been obtained and now appeared an attractive substrate to demonstrate the inertness of the Ar-CH_2-CO- group towards benzylic oxidation.



(12) (13)

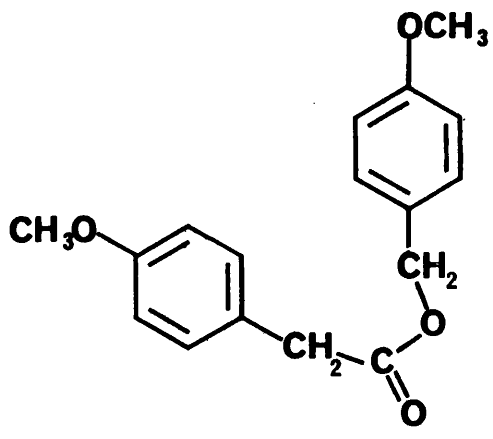
The propanone (12) was isolated as a by-product from the action of lithium aluminium hydride on the imidazolide (14) in an attempt to prepare homoveratraldehyde by the general method outlined by Staab[12]. Shown below is



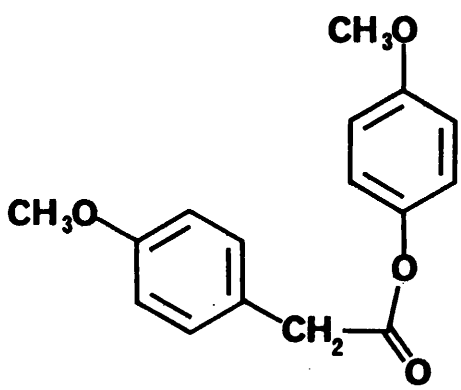
(14)

one of several alternative mechanisms by which the propanone (12) may be formed and we assume the isolation of this product is just another example of abnormal reaction of substrates containing a veratryl nucleus[13,14].

During this study, two other esters (15) and (16) were oxidized; both caused filming problems at the anode.



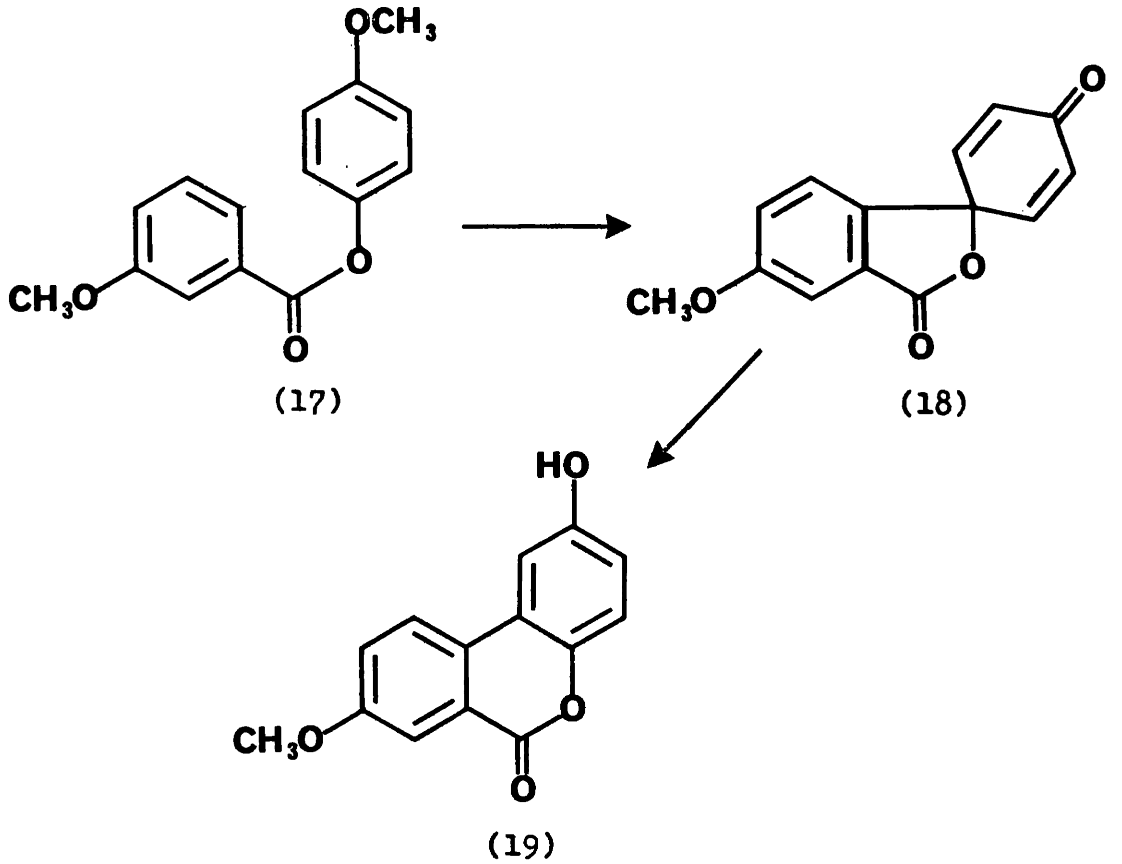
(15)



(16)

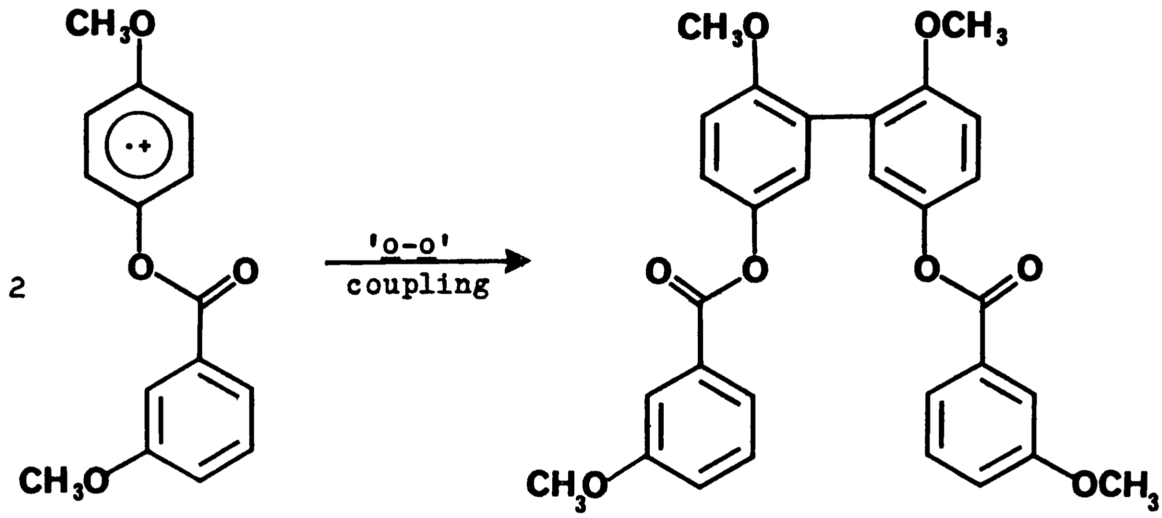
Neither is a reasonable substrate for oxidation on steric grounds, but it is noteworthy that of all the compounds studied the electrode was fouled most rapidly by the ester (15). Indeed the electrode potential at a current density of 0.35 mA/cm^2 (5×10^{-2}M concentration) under galvanostatic conditions rose from 1.45v to over 2.00v in under 50 seconds.

The anodic oxidation of 4-methoxyphenyl-3-methoxybenzoate (17) does not suffer from filming problems and at an early stage we speculated a dienone product (18) or rearranged derivative (19) might result through intramolecular coupling.



The oxidation of the ester (17) was conducted at an electrode potential of 1.40v and arbitrarily discontinued after the passage of 2F mol^{-1} of current. The orange transluscent oil obtained on work-up was subjected to column chromatography which afforded three pure components. The first product proved to be m-anisic acid and its formation is discussed later.

Mass spectrometry of the second compound (m.p. 114°-115°) showed a molecular ion peak at m/e 514; strong evidence that this product was a "dimer" of the starting material. The infra-red spectrum closely resembled that of the starting ester, but two carbonyl bands were exhibited at 1732 cm^{-1} and 1725 cm^{-1}. The ^{1}H nmr spectrum was also similar to that of (17) but close examination of the aromatic splitting pattern and analysis of the coupling constants showed that two m-anisoyl fragments remained intact while only three proton resonances of the 4-methoxyphenyl moiety were present. It was therefore apparent that the symmetrical "dimer" (21) had been formed.

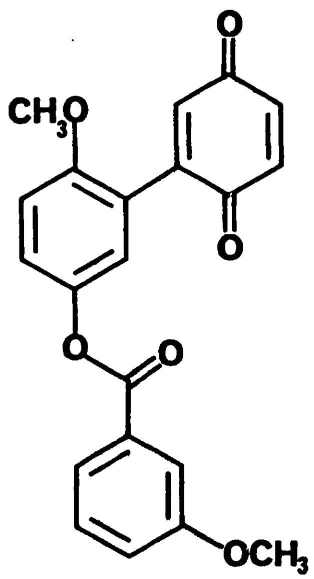


(20) (21)

Thus it would appear that at the potential at which this electrolysis was conducted only the mono cation radical (20) was formed. This conclusion is in line with our previous observation concerning the deactivating influence of a carbonyl group, with the result that the m-anisoyl unit is less easily oxidised than the p-methoxyphenoxyl moiety.

The isolation of products derived from ortho-ortho coupling of aryl radical catianic intermediates is quite rare, although ortho-ortho coupling of phenols has been reported on several occasions[15,16]. The mechanism of the latter transformations, however, involves attack of unoxidized phenolic nuclei on phenoxonium ions[17] and therefore cannot be directly equated to radical radical coupling. We assume that the ester group has a strong directing influence on the spin density of the odd electron in cation radical (20) for its behaviour is quite different to that of, say, 1, 4-dimethoxybenzene which reacts slowly in the 1 and 4 positions[18].

The third product isolated from the reaction was an orange oil, which slowly crystallized (6 days) to a dark red solid. The mass spectrum revealed a major ion peak at m/e 364 (M^+) and a large fragmentation peak at m/e 135 which corresponds to the loss of an m-anisoyl unit. The ^1H nmr spectrum is reproduced on page 233 and an analysis of the aromatic region confirmed the presence of an unsubstituted m-anisoyl subunit. The remaining resonances in the aromatic region may be accounted for by assuming that coupling has occurred through the 4-methoxyphenyl group of the starting ester and <u>ortho</u> to the methoxy group. The infra-red spectrum (page 234) indicated that two carbonyl groups were present: bands at 1735 cm^{-1} and 1655 cm^{-1}, the former arising from an ester linkage. A weaker absorption at 1610 cm^{-1} shows that olefinic groups were present and on this collective evidence we felt confident in ascribing structure (22) to the compound.



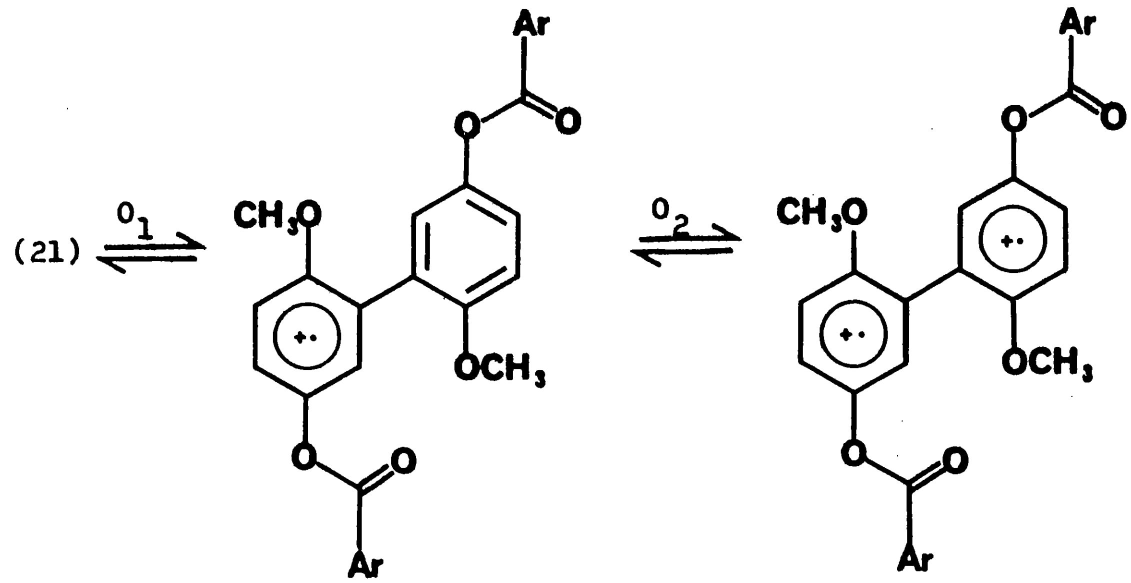
(22)

Cyclic voltammetry in conjunction with further preparative experiments were used to establish the mechanism of the formation of all three products isolated from this reaction. The cyclic voltammogram of the ester (17) (page 246) at 250 mV/sec showed on the first scan, two, one electron oxidative peaks at 1.33v (O_1) and 1.57v (O_2) and on the reverse scan, a large reductive peak at 1.56v (R_2), indicating that the second electron transfer giving rise to O_2 was largely reversible. A rapid "follow up" chemical reaction is suggested after the anodic peak (O_1) as only a correspondingly small reductive peak (R_1) was present. (The peaks O_1 and O_2

were shown to arise from the oxidation of 4-methoxyphenyl and 3-methoxybenzoyl fragments respectively by a comparison of the peak potentials of 4-methoxyphenyl-acetate and m-anisic acid). On second and subsequent scans the peak potential for O_1 was reduced to 1.30v and its intensity was also lowered, O_2 was largely unchanged. The use of potential scan cyclic voltammetry (P.S.C.V.) on the ester (17) with a holding potential 1.40v produced a further oxidative peak at 0.72v which was irreversibly coupled to a broad reductive peak at 0.30v: this behaviour has been described before as evidence for a quinone type intermediate or product.

Cyclic voltammetry of the "dimer" (21) (page 246) showed two, one electron peaks at 1.29v (O_1) and 1.45v (O_2) followed by a two electron oxidation at 1.55v (O_3). The last peak, by comparison with the voltammogram obtained for the ester (17), can be attributed to the removal of two electrons from the two m-anisoyl rings. We assume that the peaks O_1 and O_2 in this voltammogram are due to the formation of the mono cation radical (23) and the dication diradical (24) respectively. The second electron transfer (O_2) is more difficult due to the adjacent cationic species.

Interestingly, the use of P.S.C.V. with a holding potential of 1.45v, results in the formation of a fourth oxidative peak (O_4) at 0.74v (page 246) which corresponds to O_3 in the voltammogram of the ester (17). However, P.S.C.V. of (21) with a holding potential at O_1 failed to produce this peak. This is strong evidence that the mono cation radical (27) is stable in solution and that water only attacks

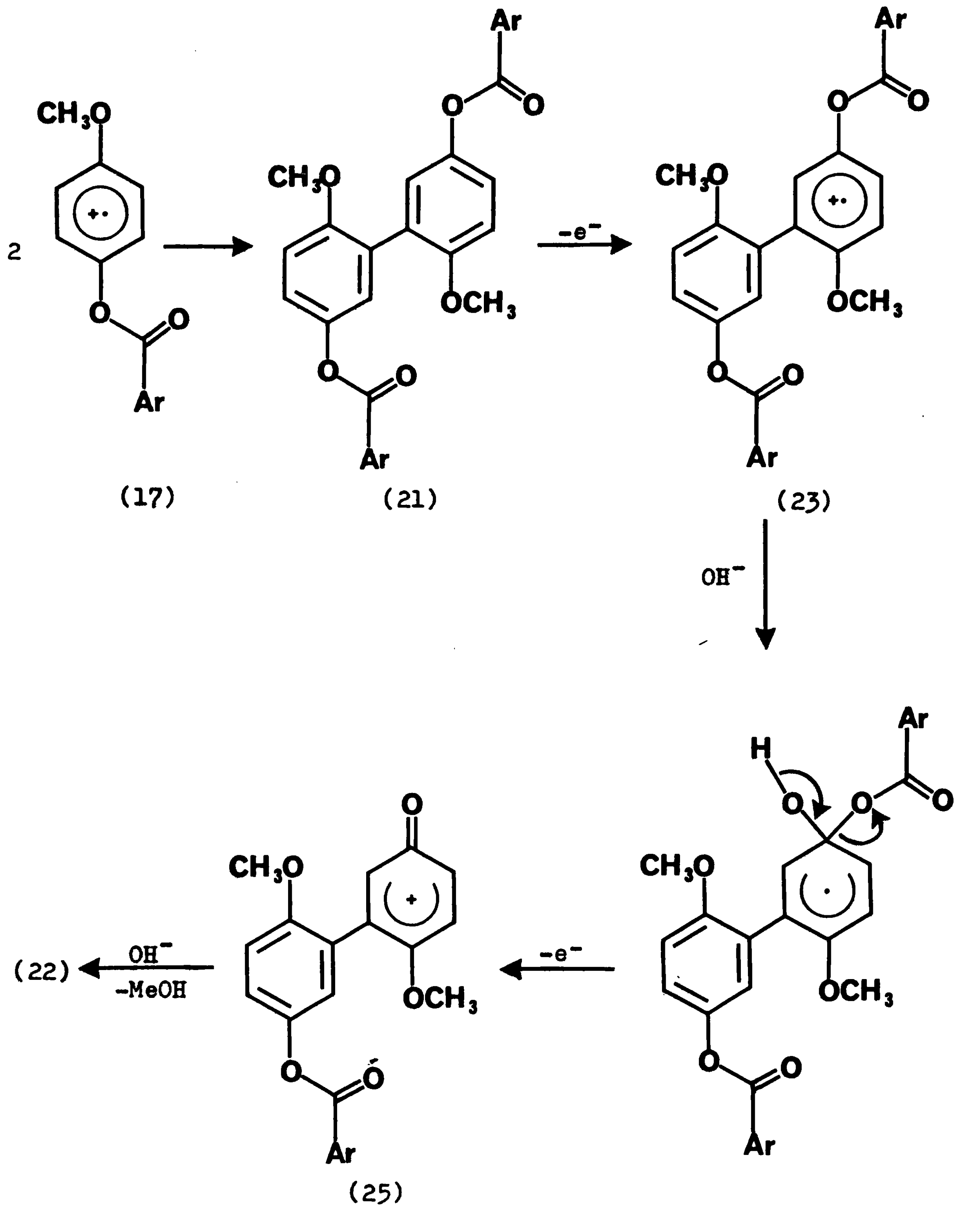


(23) (24)

Ar = 3-methoxyphenyl

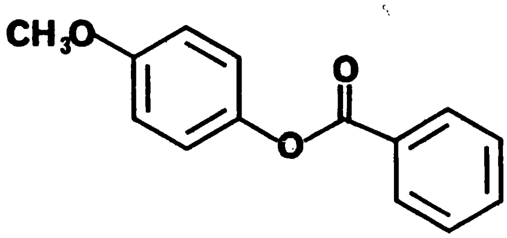
the dication diradical (24), at least on the timescale of the voltammetric measurement. Indeed, the first oxidative peak (O_1) was highly reversible (at 250 mV/sec) as long as the switching potential remained below O_2, but it would be foolish to predict that the dication diradical is necessary for quinone formation in the preparative experiment as the long term stability of (23) towards nucleophiles is unknown. In order to confirm that the quinone (22) is formed by oxidation of the dimer (21), further preparative experiments were conducted. The anodic oxidation of the ester (17) at low current densities until 1F mol^{-1} of current had been consumed resulted in formation of the dimer (21) in 64% yield. In turn, oxidation of this product (21) at 1.35v (vs S.C.E.) until 2F mol^{-1} of current had passed gave the quinone (22) in over 85% yield (estimated by gas chromatography, OV1 t = 250^{o}C f = 60 cml/min). This last experiment also shows that the diradical-dication (24) is not necessary for quinone formation and hence the reaction proceeds by a familiar stepwise E.C.E. type process. The probable mechanism for the formation of all the observed products is outlined in Scheme 2.

Scheme 2



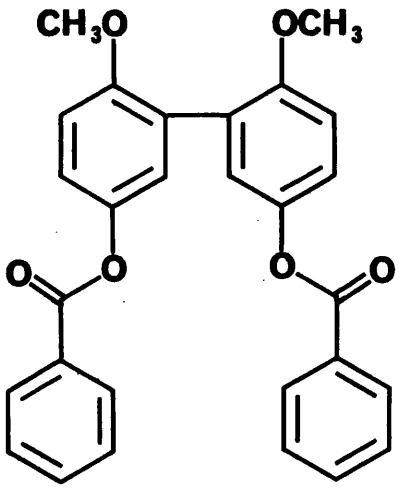
Ar = 3-methoxyphenyl

It seemed unlikely that the m-anisoyl fragment was involved in the reaction in any way, but to confirm this point and test the general applicability of the reaction, the preparative oxidation of 4-methoxyphenylbenzoate (26) was undertaken.

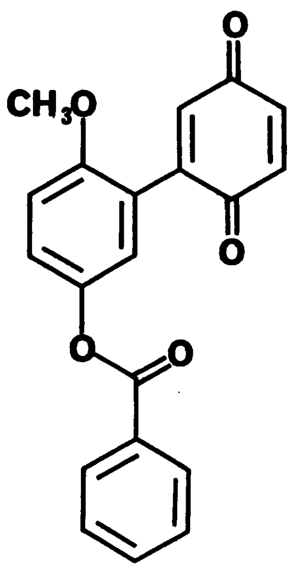


(26)

The electrolysis of (26) proceeded smoothly at 1.35v (vs S.C.E.) until 1F mol^{-1} of current had been utilized. On work-up pale yellow crystals were shown to be the dimer (27). The anodic oxidation of (27) (2F mol^{-1} utilization) gave both benzoic acid and the quinone (28).

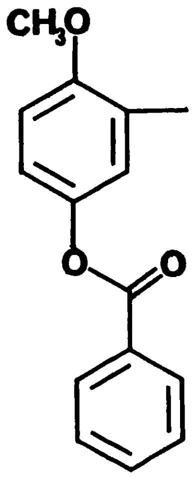


(27)

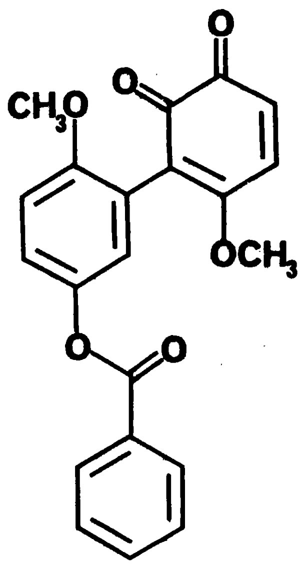


(28)

One further product was isolated in small quantity. This was an orange-red solid which showed a molecular ion peak at m/e 364 and a base peak at m/e 105. The latter corresponds to a benzoyl fragment. The ^{1}H nmr spectrum of this compound is reproduced on pages 235 and 236 , and together with the infra-red spectrum (page 237) we concluded that the compound had the following part structure.



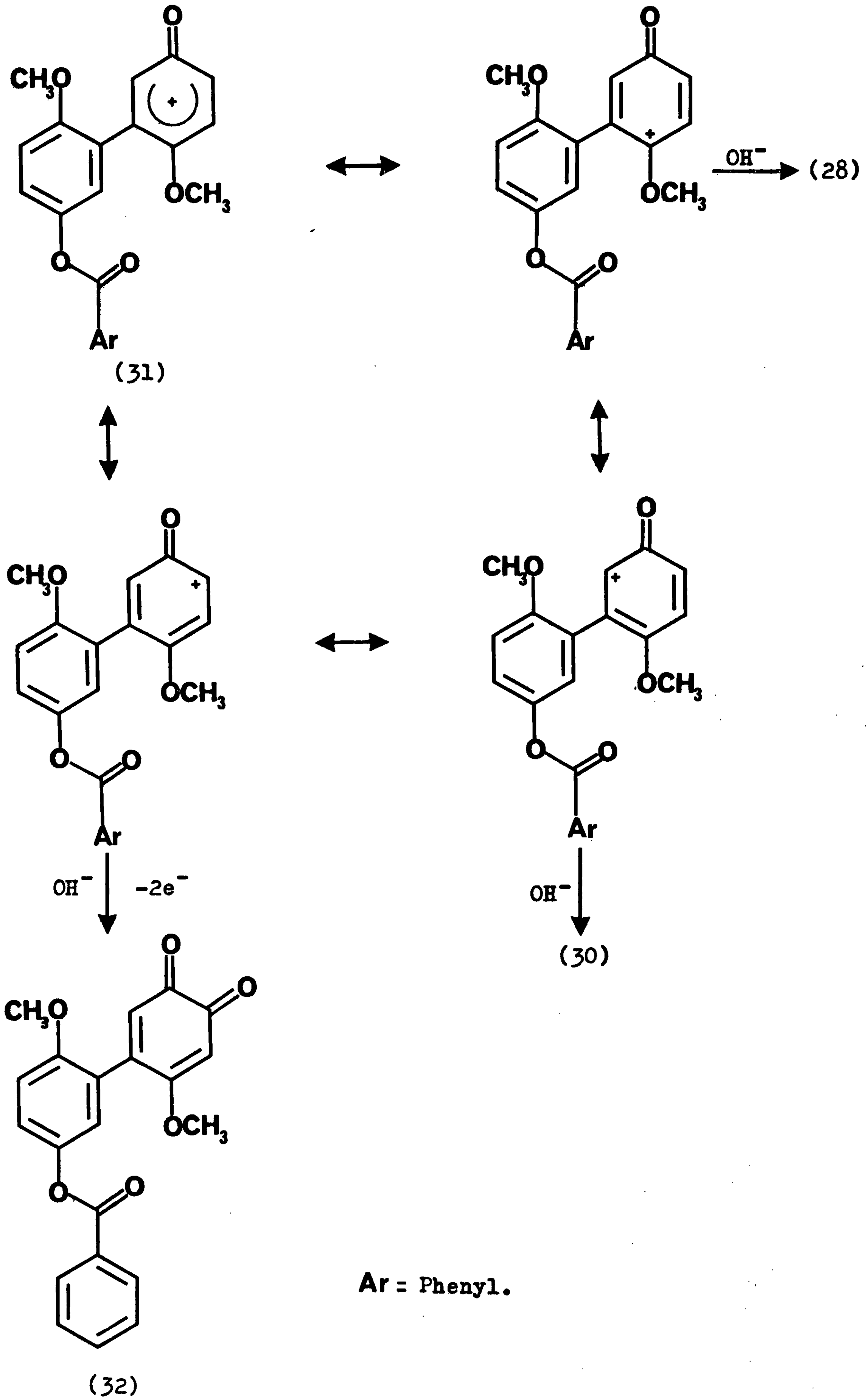
The three strong absorptions in the infra-red spectrum at 1735, 1678 and 1642 cm^{-1} were attributable to carbonyl absorptions with the 1735 cm^{-1} peak arising from the ester linkage of (29). From the previous results it seemed probable that a quinone of sorts was present and the two olefinic coupled protons (J =3.75Hz) at $\delta = 5.98$ and $\delta = 6.78$ in the ^{1}H nmr spectrum indicated an unsymmetrical quinone. With a knowledge of the molecular ion we were able to make the structural assignment (30). The formation of this product rationalized when consideration of the intermediate (25) of Scheme 2 was taken into account.



(30)

Assuming that the mechanisms for the anodic oxidation of the esters (17) and (26) are identical, then the electrolysis of (26) will result in the intermediate (31) which undergoes nucleophilic attack by water.

All of the observed products may be raionalized through demethylation or nucleophilic attack (by water) upon the carbonium species (31). Moreover, the product ratios reflect, to a degree at least, the comparative stabilities of the resonance contributors. A detailed examination of the ^{1}H nmr spectrum of (30) reveals two peaks at $\delta = 6.04$ and $\delta = 6.85$ of uncertain origin and we feel sure that these singlet resonances arise from the ortho quinone (32).



Ar = Phenyl.

Summary:

The first and third chapters of this thesis demonstrate practically the effect that adverse stereochemistry and instability of intermediates can have on yields of intramolecularly coupled products. From our results on the oxidation of substrates containing two aryl nuclei joined by a simple chemical link, it appears that certain basic structural requirements are necessary for successful intramolecular cyclization.

1. Preferably both rings should possess a similar oxidation potential.

2. Favourable geometry is mandatory in order to allow close approach of the two radical cations.

3. The intermediate dication diradical must be sufficiently stable to negate the possibility of interceding chemical reactions before radical coupling can occur; in particular, the molecule should not contain benzylic protons which possess a high intrinsic acidity.

4. The substrate should not contain any other electroactive group within the potential range of the experiment besides the two aryl nuclei.

The second chapter illustrates the way in which the technique of anodic oxidation may be applied to simple heterocyclic systems to produce novel compounds that would be inaccessable by normal chemical procedures.

Experimental

Experimental to Chapter 1

U.V. spectra were recorded on a Perkin Elmer 402 spectrometer for solutions in aqueous 95% ethanol; a Perkin Elmer 237 machine was used to record IR spectra and the data refer to Nujol mulls. The ^{1}H nmr spectra were recorded at 100 MHz on a JEOL PS 100 spectrometer using tetramethylsilane as an internal standard and mass spectroscopic data were obtained using a AEI MS 12 instrument.

All electrolyses were conducted with an H-type cell with an anolyte capacity of 150cm^3. Unless stated otherwise, acetonitrile (distilled from phosphorus pentoxide under dry nitrogen) was used as the solvent and anhydrous sodium perchlorate (dried under reduced pressure at 125°C for twenty-four hours)formed the supporting electrolyte. A platinum gauge ($\sim$60cm^2) was used as the anode with a mercury pool forming the counter electrode. The electrode potential was monitored by a calomel electrode connected to the cell via an agar/potassium chloride conducting bridge and the current was provided by a Farnell stabilized power supply.

A typical preparative experiment was conducted by dissolving $\sim$1g of substrate in the anolyte and the external supply voltage increased until either a predetermined electrode potential was reached, or a practical current flow (15-60mA) was obtained. When the appropriate amount of current had been consumed the anolyte was poured into water ($\sim$600cm^3) and the solution extracted with dichloromethane. The combined, dried, organic extracts were evaporated to give the crude anodic product, after which normal separation procedures were followed.

All cyclic voltammograms were recorded using a 'home-built' three electrode polarograph constructed from a circuit diagram supplied by Dr J.H.P. Utley of Queen Mary College, London. Voltammograms were displayed on either a Telequipment 261A oscilloscope or Hewlett Packard flat bed X-Y recorder (1 sec. pen response). Platinum wire or platinum bead micro-electrodes were used as anodes for voltammetric measurements in a simple three electrode cell (see page 23).

Veratraldoxime (5)[45]

Veratraldehyde (20g, 0.12mol) and hydroxylamine-hydrochloride (20g, 0.29mol) were heated in a solution of ethanol ($200cm^3$) and pyridine ($20cm^3$) for 2h. Evaporation of the solvents followed by partition of the crude product between chloroform-water gave on evaporation of the chloroform extracts a solid (20.06g, 92%) m.p. 94°C; νmax 3460, 1608, $1586cm^{-1}$.

Veratrylamine[45]

Raney alloy (35.0g) was added in 5g portions to a stirred solution of veratraldoxime (18 g,0.1mol) in ethanol ($450cm^3$) and 2N sodium hydroxide ($450cm^3$). The solution was stirred for one hour, extracted with chloroform ($3 \times 200cm^3$) and the combined extracts were then washed with water, and evaporated to give a colourless oil which was purified by distillation under reduced pressure (12.6g, 76%), $b_{2.5-3}$ 120°C, νmax 3450, 3400, 1605, $1598cm^{-1}$.

N-Homoveratroyl-veratrylamine (6)[5]

Veratrylamine (5.0g, 0.03mol) and homoveratroyl chloride[6] (6.40g, 0.03mol) were heated in a solution of dry benzene

($50cm^3$) and pyridine ($5cm^3$) for 3h. The solution was cooled and washed with water ($2 \times 100cm^3$) followed by evaporation of the solvent to give prisms (7.4g, 72%), m.p. 130°C, ν max 3320, 1640cm^{-1}; δ (CD_3CN) 3.40 (2H, s), 3.70 (3H, s, OMe), 3.75 (9H, s, 3 x OMe), 4.26 (2H, d, J = 6Hz), 6.75 - 6.91 (6H, m, Ar), 6.90 (1H, s, deut); m/e 345 (M^+).

3, 4-Dimethoxycinnamic acid (9)[47]

Veratraldehyde (30g, 0.18mol) and malonic acid (38g, 0.33mol) were dissolved in a solution of pyridine ($100cm^3$) and piperidine ($3cm^3$). The solution was stirred at 80°C for 1½h. followed by 2h. at 100°C. On cooling the solution was poured into water ($500cm^3$) containing concentrated hydrochloric acid ($170cm^3$) and the flocculent white solid filtered, washed with a little ethanol and dried to give a powder (32.0g, 85%), m.p. 168-170 (lit.,[47] 169°C); ν max 3100-2500, 1675, 1624, 1596cm^{-1}, m/e 208 (M^+).

β-(3, 4-Dimethoxyphenyl) propionic acid

The acid (9) (10g, 0.048mol) was dissolved in dimethylformamide ($300cm^3$) in the presence of Pd/C (10%, 0.1g). The resulting solution was shaken under hydrogen (150p.s.i.) at 40°C for 6h. and filtered through Kieselguhr. Evaporation of the solvent gave a colourless powder. (9.70g, 96%), m.p. 96-97°C; ν max 3200-2250, 1695, 1610cm^{-1}; δ ($CDCl_3$) 2.70 (2H, t, J = 7Hz), 2.92 (2H, t, J = 7Hz), 3.87 (6H, s, 2 x OMe), 6.70-6.84 (3H, m, Ar), 11.0 (1H, s); m/e 210 (M^+).

<u>2-(3, 4-Dimethoxyphenyl)-N-(3, 4-dimethoxybenzyl) propionamide</u> (10)

β-(3, 4-Dimethoxyphenyl) propionoyl chloride (8g, 0.035mol) and veratrylamine (5.8g, 0.035mol) were reacted together by the same route as for the preparation of (6) to give prisms (9.9g, 79%), m.p. 129-130°C (from ethanol); ν max 3480, 1640, 1600cm^{-1}; <u>m/e</u> 359 (M^+).

<u>N-Homoveratryoyl-homoveratrylamine</u> (11)

Homoveratrylamine (10g, 0.055mol) and homoveratroyl chloride (11.8g, 0.055mol) were reacted as described for (6) to give colourless crystals (16.17g, 82%) m.p. 119°C; ν max 3320, 1640, 1540cm^{-1}, δ ($CDCl_3$) 2.69 (2H, t, $\underline{J}$ = 7Hz), 3.42 (2H, t, $\underline{J}$ = 7Hz), 3.47 (2H, s), 3.85 (12H, s, 4 x OMe), 5.69 (1H, s), 6.50-6.80 (6H, m, Ar); <u>m/e</u> 357 (M^+).

<u>3, 4-Dimethoxybenzal-3, 4-dimethoxyphenylethylamine</u> (15)

Homoveratrylamine (10.0g, 0.055mol) and veratraldehyde (9.2g, 0.055mol) were heated under reflux in dry xylene (30cm^3) under azeotropic conditions in the presence of a catalytic amount of <u>p</u>-toluenesulphonic acid for three hours. Evaporation of the solvent gave an oil which triturated in pet. ether b.p. 60-80. (17.1g, 94%), m.p. 81°C, ν max 1630, 1600cm^{-1}.

<u>Veratrylhomoveratrylamine</u>

The imine (15) (10g, 0.03mol) was heated in a solution of ethanol (100cm^3) containing sodium borohydride for 15 minutes. Excess sodium borohydride was destroyed by the addition of acetone and the solution was poured into dilute hydrochloric acid and extracted with dichloromethane.

Basification with sodium hydroxide (0.1M) followed by re-extraction with dichloromethane gave on evaporation of the organic solvent an oil which promptly solidified to give prisms (8.9g, 89%), m.p. 79-80°C (lit[14]., 79°C); ν max 1610, 1595cm^{-1}; m/e 331 (M^+).

N-Veratryl-N-homoveratrylacetamide (14)

Veratrylhomoveratrylamine (5.0g, 0.015mol) was dissolved in a solution of ethyl acetate (20cm^3) and acetic anhydride (1.73g, 0.017mol) and stirred at room temperature for 1h. Evaporation of the solvents followed by trituration in pet. ether gave a colourless powder (5.3g, 94%), m.p. 81-82°C (ethanol); ν max 1640, 1595cm^{-1}, δ (DMSO) 1.90 and 2.01 (2H, ratio 2:1, N-$COCH_3$) 2.70 (2H, t, J = 8Hz), 3.36 (2H, t, J = 8Hz), 3.70 (12H, s, 4 x OMe), 4.38 and 4.42 (2H, ratio 1:2, Ph-CH_2-N_1-), 6.60-6.90 (6H, m, Ar), m/e 373 (M^+).

6-Acetyl-5, 6, 7, 8-tetrahydro-2, 3, 10, 11-tetramethoxydibenz [c, e] azocine (16)[48]

The imine (15) (2g) and anhydrous sodium carbonate (1g) were added to the anode compartment and electrolysed at a controlled anode potential of 1.15v until 1.9F mol^{-1} of current had been consumed. Work-up of the anolyte as described on page 189 afforded a gum which was triturated with ethanol to give the azocine (16) (1.31g, 66%), m.p. 190°C (ethanol-ether); λ max 215, 259 and 283 nm; ν max 1665 sh, 1630, 1600cm^{-1}, δ ($CDCl_3$) 2.18 (3H, s, Ac), 3.10 (1H, d, J = 14Hz) and 5.30 (1H, d, J = 14Hz) (5-Hz), 2.22-3.40 (4H, m, 7- and 8-Hz), 3.95 (12H, s, 4 x OMe), 6.88 (1H, s), 6.90 (1H, s), 6.95 (1H, s), 7.60 (1H, s); m/e 371 (M^+), 357, 356, 299. (Found: C, 67.9; H, 6.7; N, 3.7 $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8;

N, 3.8%)

6-Ethyl-5, 6, 7, 8-tetrahydro-2, 3, 10, 11-tetramethoxydibenz [c, e] azocine (17)[48]

The product (16) (0.5g) was dissolved in tetrahydrofuran ($50cm^3$) and an excess of lithium aluminium hydride was added. The mixture was heated under reflux for 3h., the excess reagent was destroyed with ethyl acetate, water was added and the mixture was extracted with chloroform. The extracts were evaporated to yield compound (17) as a gum which triturated with ether; (0.40g, 83%), m.p. 95-96°C λ max 214, 258 and 283nm; ν max 1600, $1505cm^{-1}$; δ ($CDCl_3$) 1.10 (3H, t, $\underline{J}$ = 6Hz, Me), 2.2-4.0 (8H, m, 4 x CH_2) 3.80-4.00 (12H, 2 x s, 4 x OMe), 6.75-7.00 (4 x 1H, aromatic). (Found: C, 70.5; H, 7.6; N, 3.9 $C_{21}H_{27}NO_4$ requires C, 70.6; H, 7.6; N, 3.9%).

N-Methyl-veratrylamine

Veratraldehyde (20g, 0.12mol) was dissolved in a solution of ethanol ($250cm^3$) and methylamine (30% solution, 0.36mol) and shaken under hydrogen (80 p.s.i.) for 8h. The solvent was evaporated to leave an oil which was taken up in hydrochloric acid (0.1M) and extracted with dichloromethane. The solution was basified with sodium hydroxide, and re-extracted with dichloromethane, which gave on evaporation, a colourless oil (14.9g, 74%), b_{10} 140-145°C (lit[49]., b_{11} 143-150°C) ν max 3300, $1605cm^{-1}$.

N-Methyl-N-veratryl-3, 4-dimethoxyphenylacetamide (18)

N-Methylveratrylamine (6.23g, 0.037mol) and homoveratroyl chloride (8.0g, 0.037mol) were reacted together in a similar way to that described for the preparation of (6), to give the title compound (11.0g, 82%), m.p. 64-66°; ν max 1640, 1607, 1594cm^{-1}, δ ($CDCl_3$) 2.91 (3H, s), 3.80 (2H, s), 3.86 (12H, s, 4 x OMe), 4.5 and 4.9 (2H, 2 x s, Ar-CH_2-N-), 6.80-6.90 (6H, m, aromatic); m/e 359 (M^+), 287, 224, 151.

5, 8-Dihydro-2, 3, 10, 11-tetramethoxy-6-methyldibenz [c, e] azocine 7 (6H)-one (19)[48]

Conditions for the electrolysis of (18) were similar to those described for the amide (15). Similar work-up procedures gave the azocine (19) (45%), m.p. 204-205°C (ethanol); λ max 218, 235sh, 265, 283 nm; ν max 1640, 1605, 1510cm^{-1}; δ ($CDCl_3$) 3.20 (3H, s, NMe), ca 3.9 br (16H, s, 5- and 8-H_2 and 4 x OMe), 6.90-6.95 (4 x 1H, s, aromatic) (Found: C, 66.0; H, 6.7; N, 3.9 $C_{19}H_{23}NO_5$ requires C, 66.1; H, 6.7; N, 4.1%).

5, 6, 7, 8-Tetrahydro-2, 3, 10, 11-tetramethoxy-6-methyldibenz [c, e] azocine (21)[48]

The azocine (19) (0.75g, 0.0021mol) was heated with an excess of lithium aluminium hydride in tetrahydrofuran for four hours. Normal work-up procedures gave the azocine (21) as prisms (57g, 80%), m.p. 136-138° (from ether); λ max 214, 258, 283 nm; ν max 1600, 1505cm^{-1}, δ ($CDCl_3$) 2.50 (3H, s, NMe), 2.55 (2H, t, J 8H_2, 7-H_2), 3.08 (1H, d, J 14H_2) and 3.52 (1H, d, J 14H_2) (5-H_2), 3.20 (2H, t, J 8H_2, 8-H_2), 3.90 (12H, s, 4 x OMe), 6.70-6.86 (4 x 1H, s, aromatic) (Found: C, 69.9, H, 7.2; N, 4.2, $C_{20}H_{25}NO_4$ requires C, 69.95; H, 7.3; N, 4.1%).

N-Methyl-N-veratryl-3, 4-dimethoxybenzamide (22)

N-Methyl-veratrylamine (8.0g, 0.044mol) and veratroyl chloride (8.8g, 0.044mol) were reacted together in the manner described for (6) to give the title compound as a powder (11.7g, 77%), m.p. 102-103°C, ν max 1630, 1600, 1580cm^{-1}; δ ($CDCl_3$) 2.94 (3H, s), 3.83 (12H, 4 x OMe), 4.52 (2H, s), 6.70-7.10 (6H, m, aromatic); m/e 345 (M^+), 330, 180, 151.

<u>6, 7-Dihydro-2, 3, 9, 10-tetramethoxy-6-methyldibenz [c, e] azepine-5-one</u> (23)

The electrolysis of (22) (2.0g, 0.0058mol) was conducted at an electrode potential of 1.15v (vs SCE) until 1.5F mol^{-1} of current was consumed gave a crude product which on subjecting to column chromatography (SiO_2/ethyl acetate, pet. ether) gave colourless prisms (0.04g, 2%), m.p. 220-221°C (ethanol); λ max 218, 248, 282 nm; ν max 1618, 1600, 1583cm^{-1}; δ ($CDCl_3$) 3.02 (3H, s). 3.80-3.90 (12H, 2 x s, 4 x OMe), 4.35 (2H, s), 6.90 (1H, s), 6.92 (2H, s), 7.01 (1H, s); m/e 343 (M^+), 314 (60), 165 (20), 150 (20) (Found C, 66.5; H, 6.2; N, 4.2 $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%).

<u>N-(4-Methoxybenzyl)-N-(3-methoxyphenylethyl)-acetamide</u> (26)

This amide was prepared by standard methods, eg, those already outlined for the amide (14); thus the title compound was prepared from p-anisaldehyde and m-homoanisylamine in an overall yield of 74%. ν max 1640, 1605, 1595cm^{-1}; δ ($CDCl_3$) 2.00 x 2.12 (3H, 2 x s, $COCH_3$), 2.72 (2H, t, J 7.5H_2), 3.46 (2H, t, J 7.5H2), 3.73 (6H, s, 2 x OMe) 4.31 x 4.55 (2H, 2 x s, Ph-CH_2-N), 6.6)-7.40 (8H, m, aromatic).

<u>4-Hydroxyphenylacetate</u>

The amide (26) (1.0g, 0.0032mol) was electrolysed in an acetonitrile/sodium perchlorate electroyte system using a carbon felt anode, at a steady electrode potential of 1.38v

2F m^{-1}. Normal work-up procedures, followed by column chromatography (SiO_2/ethylacetate, pet. ether, 1:1) gave 4-hydroxyphenylacetate as an oil (150mg), ν max 3400, 1730, 1600, 1500cm^{-1}; δ ($CDCl_3$) 2.20 (3H, s), 6.00-6.80 (1H, bs, -OH), 6.60 (2H, d, _J_ 9Hz), 6.80 (2H, d, _J_ 9Hz); m/e 152 (M^+), 110 (100), 81 (10).

N-(3-Methoxyphenylethyl)-4-methoxyphenylacetamide (30)[40]

4-Methoxyphenylacetic acid (10.0g, 0.066mol) was stirred with N, N-diimidazole (10.7g, 0.066mol) in dry tetrahydrofuran (100cm^3) for 30 minutes at room temperature. To this solution was added m-homoanisylamine (10.0g, 0.066mol) in tetrahydrofuran (100cm^3) and the solution stirred for one hour. Evaporation of the solvent gave an oil which was separated between chloroform/water. The chloroform layer was washed several times with water and evaporated to give a colourless powder (16.3g, 82%), m.p. 80-81°C (lit[40]., 80-82°C) ν max 3450, 1640, 1611, 1595cm^{-1}, δ ($CDCl_3$) 2.65 (2H, t, _J_ $6H_2$), 3.35 (2H, t, _J_ = 6Hz), 3.40 (2H, s), 3.70 (3H, s, OMe), 3.74 (3H, s, OMe), 5.60 br (1H, s, deut[3]), 6.50-7.20 (8H, m, aromatic).

N-(3-Methoxyphenylethyl)-N-(4-methoxyphenylethyl)acetamide (31)

The amide (30) (6g, 0.02mol) in dry tetrahydrofuran (20cm^3) was added dropwise to a solution of diborane in tetrahydrofuran (1.0M) (60cm^3, 0.06mol) and the mixture refluxed for one hour. On cooling, the solution was poured into dilute hydrochloric acid (1.0M, 200cm^3) and stirred for one hour followed by addition of sodium hydroxide (30%) until the solution was alkaline. The combined dichloromethane extracts of this solution were washed with water and evaporated to give N-m-homoanisyl-p-homoanisylamine as an oil (5.0g, 89%). This product (4.0g, 0.014mol) was stirred in a solution of ethyl acetate ($25cm^3$) containing acetic anhydride (3g, 0.03mol) for one hour. Evaporation of the solvents gave the title compound as an oil in almost quantitative yield. ν max 1640, 1610, $1600cm^{-1}$, δ ($CDCl_3$) 1.88 (3H, s), 2.5-3.0 (4H, m), 3.10-3.70 (4H, m), 3.74 (5H, 2 x OMe), 6.60-7.40 (8H, m, aromatic); m/e 327 (M^+).

Bis-4, 4^1, 5, 5^1-tetramethoxybiphenyl-2, 2^1-dipropionic acid (33)

β -(3, 4-Dimethoxyphenyl)propionic acid (1.5g, 0.0071mol) was electrolysed at + 1.1v in acetonitrile/trifluoroacetic acid (4:1) with sodium perchlorate as the supporting electrolyte until 1F mol^{-1} had been utilized. Work-up of the anolyte by the usual method gave oil which slowly crystallized to give prisms (0.82g, 55%), m.p. 145°C (from ethanol), λ max 227 sh, 287 nm; ν max 3500, 3300, 2650, 2400, 1682, $1602cm^{-1}$; δ ($CDCl_3$) 2.36 (4H, t, J=7Hz), 2.65 (4H, t, J=7Hz), 3.81 (6H, s, 2 x OMe), 3.89 (6H, s, 2 x OMe), 5.60-6.30 (4H, t, s, H_2O + 2COOH), 6.64 (2H, s), 6.83 (2H, s), m/e 418 (M^+), 299, 286.

Dimethyl 4, 4^1, 5, 5^1-tetramethoxybiphenyl-2, 2^1-dipropionate (34)

p-Tolylsulphonylmethylnitrosamide (6.42g) in dry ether ($90cm^3$) was cooled in an ice bath and a solution of potassium hydroxide (1.2g) in ethanol ($30cm^3$) was added dropwise. After 5 minutes the mixture was distilled to give an ethereal solution of diazomethane[50]. The carboxylic acid (33) (0.75g, 0.0018mol) was added to this solution and left overnight. Excess reagent was destroyed and the solution partitioned between dichloromethane/water, and the dichloromethane layer separated, dried ($Mg\ SO_4$) and evaporated to give the title compound as prisms (0.71g, 89%) m.p. 110-111°C (from ether/ethanol); λ max 1725, 1603, 1507cm^{-1}; δ ($CDCl_3$) 2.50 (4H, t, *J* 7Hz), 2.67 (4H, t, *J* 7Hz), 3.65 (6H, s, 2 x COOMe), 3.89 (6H, s, 2 x OMe), 2.96 (6H, s, 2 x OMe), 6.71 (2H, s), 6.87 (2H, s); *m/e* 446 (M^+), 416 (15), 299 (45); (Found C, 64.4; 6.6. $C_{24}H_{30}O_8$ requires C, 64.5; H, 6.7%).

<u>2, 2′-Di(N-acetylethylamino-4, 4′, 5, 5′-tetramethoxybiphenyl</u> (36)

The electrolysis of N-acetylhomoveratrylamine (35) was conducted in the same way to that described for the preparation of (33). The yield of (36) after column chromatography (alumina, chloroform, pet. ether) was 26%, m.p. 188-190°C (ethanol), ν max 3280, 3080 (weak), 1650, 1600cm^{-1}, δ ($CDCl_3$) 1.84 (6H, s, 2 x $COCH_3$), 2.50 (4H, m), 3.20 (4H, m), 3.75 (6H, s, 2 x OMe), 3.82 (6H, s, 2 x OMe), 6.00 (2H, bs), 6.52 (2H, s), 6.71 (2H, s); *m/e* 444 (M^+), 385, 299, 151. (Found: C, 64.9; H, 7.3; N, 6.1 $C_{24}H_{32}O_6N_2$ requires: C, 64.8; H, 7.3; N, 6.3%).

Experimental for Chapter 2

2-Nitro-4, 5-dimethoxyphenylacetic acid[13]

Homoveratric acid (40g, 0.2mol) was added in 2g portions to a stirred solution of concentrated nitric acid (200cm^3) maintaining the temperature between 0-10°C. After the final addition, the mixture was stirred for 5 minutes and poured into water 800cm^3 and the precipitate filtered, washed with water and dried to give a pale yellow powder (40.3g, 82%), m.p. 209-210°C (ethanol, lit[13]., 206-208°C), ν max 3200-2930, 1690, 1620 (weak), 1585cm^{-1}.

Ethyl 2-nitro-4, 5-dimethoxyphenylacetate (10)

2-Nitro-4, 5-dimethoxyphenylacetic acid (20g, 0.082mol) was heated in a solution of absolute ethanol (250cm^3) containing concentrated sulphuric acid (20cm^3) for 2 hours. The mixture was evaporated to half volume and cooled to give pale yellow crystals which were filtered, washed with dilute sodium carbonate solution and water (20.5g, 92%), m.p. 100-101°C; ν max 1725, 1620 (weak), 1580cm^{-1}, δ ($CDCl_3$) 1.30 (3H, t, *J*=7.5Hz), 3.90 (6H, s, 2 x OMe), 4.15 (2H, q, *J*=7.5Hz), 6.70 (1H, s), 7.70 (1H, s).

Ethyl 2-amino-4, 5-dimethoxyphenylacetate (11)[14]

The nitro ester (10) (15g, 0.055mol) was dissolved in ethanol (250cm^3) and hydrogenated at (100 lb in^2) for 3 hours in the presence of a palladium-charcoal catalyst (10%, 0.1g). The solution was filtered and evaporated to give an oil which triturated with pet. ether (12.2g, 92%), m.p. 54-55°C (lit[14]., 54°C); ν max 3200, 1710, 1610cm^{-1}, *m/e* 239 (M^+), 222, 207, 193.

Ethyl 4, 5-Dimethoxy-2-(3, 4-dimethoxybenzylideneamino) phenylacetate (12)

The amino ester (11) (8.0g, 0.033mol) and veratraldehyde (5.6g, 0.033mol) were heated for two hours in dry toluene ($150cm^3$) using a Dean Stark separator. Evaporation of the solvent, followed by trituration with ether gave a brick-red coloured powder (10.9g, 84%), m.p. 94-95°C (ethanol); ν max 1730, 1720, 1680, $1620cm^{-1}$, δ ($CDCl_3$) 1.20 (3H, t, J=7Hz), 3.82 (2H, s), 4.00 (12H, s, 4 x OMe), 4.18 (2H, q, J=7Hz), 6.70-7.70 (5H, m, aromatic), 8,40 (1H, s); m/e 387 (M^+), 372, 314.

Ethyl 4, 5-Dimethoxy-2-(3, 4-dimethoxybenzylamino) phenylacetate (13)

The foregoing compound (5g, 0.013mol) in ethanol ($250cm^3$) was hydrogenated in the presence of Adams catalyst (0.1g) at 40 lb in^{-2} for five hours. The solution was filtered, and evaporated to give an oil which triturated with ether (4.4g, 89%), m.p. 89-90°C (diethyl ether); ν max 250, 284, 302 nm; δ max 3400, 1725, 1610, $1590cm^{-1}$; m/e 389 (M^+).

5, 6-Dimethoxy-1-(3, 4-dimethoxybenzyl) indolin-2-one (7)

The foregoing compound (4.0g, 0.01mol) was passed through a column containing basic alumina using chloroform as eluent. The combined fractions were collected and evaporated to give an oil which triturated with ether to give colourless prisms in almost quantitative yield, m.p. 103°C (ethanol); λ max 208, 277, 301 nm; ν max 1705, 1619, $1601cm^{-1}$; δ ($CDCl_3$) 3.48 (2H, s), 3.70 (3H, s, 1 x OMe), 3.75 (9H, s, 3 x OMe), 4.72 (2H, s), 6.30 (1H, s), 6.71 (1H, s), 6.74 (3H, m);

m/e 343 (M^+), 192, 151, (Found: C, 66.4; H, 6.2; N, 4.0. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.1; N, 4.1%).

4, 5-Dimethoxy-2-(N-trifluoroacetyl-3, 4-dimethoxybenzylamino) phenylacetate (19)

The amine (13) (4.0g, 0.033mol) was stirred at room temperature in a solution of trifluoroacetic acid ($15cm^3$) containing trifluoroacetic anhydride (10.4g, 0.049mol) for 15minutes. Evaporation of the solvents gave the title compound as an oil in almost quantitative yield, ν max 1725, 1715, 1660, $1600cm^{-1}$.

5, 6-Dimethoxy-1-(3, 4-methylenedioxybenzyl) indolin-2-one (22)

This compound was prepared by exactly the same method as the dimethoxy analogue (7) but using piperonaldehyde in place of veratraldehyde. The title compound was obtained as prisms m.p. 125-126°C (ethanol); ν max 1690, 1610, $1600cm^{-1}$; δ ($CDCl_3$) 3.42 (2H, s), 3.74 (6H, s, 2 x OMe), 4.70 (2H, s), 5.80 (2H, s, $-O-CH_2-O-$), 6.30 (1H, s), 6.65-6.75 (3H, m), 6.80 (1H, s); m/e 327 (M^+), 313 (8), 192 (12), 135 (100).

5, 6-Dimethoxy-1-(3, 4-methylenedioxybenzyl) indoline (21)

The foregoing compound (3.0g, 0.0091mol) was dissolved in dry tetrahydrofuran ($30cm^3$) and added to a solution of diborane in tetrahydrofuran (1M, $27cm^3$,) and heated under reflux for 2 hours. The flask was cooled and dry HCl gas bubbled through the stirred solution for 25 minutes and allowed to stand for 1 hour. Water ($50cm^3$) and ammonium hydroxide was added and the tetrahydrofuran distilled off to leave an aqueous solution which was extracted with dichloromethane. Evaporation of the organic extracts, followed by trituration with ether gave the title compound as prisms (0.92g, 32%), m.p. 70-72°C (ether); ν max 1605, 1600, 1500cm^{-1}; δ ($CDCl_3$) 2.90 (2H, t, J=6Hz), 3.28 (2H, t, J 6Hz), 3.84 (6H, s, 2 x OMe), 4.12 (2H, s), 5.95 (2H, s), 6.30 (1H, s), 6.70-7.00 (4H, m, aromatic); m/e 313 (M^+), 161, 151. (Found: C, 68.8; H, 6.0; N, 4.3 $C_{18}H_{19}NO_4$ requires: C, 69.0; H, 6.1; N, 4.5%).

6-Hydroxy-5-methoxy-1-(3, 4-methylenedioxybenzyl) indole (23)

The indoline (21) (0.80g, 0.0025mol) was dissolved in ether (30cm^3) and dry hydrogen chloride was passed through the solution. The ether was evaporated to leave a gum which was electrolysed in acetonitrile at an electrode potential of 1.25v (vs SCE). After the passage of 2F mol^{-1} of current, the anolyte was poured into a solution of sodium carbonate (2N, 250cm^3) and extracted with dichloromethane. The organic extracts were evaporated, and subjected to column chromatography (SiO_2, ethylacetate, pet. ether gradient), the first collected fraction yielding an oil which triturated with ether to give colourless prisms (0.11g, 15%), m.p. 90-91°C (ether); ν max 3360, 1610 (weak), 1580cm^{-1}; δ ($CDCl_3$) 3.82 (3H, s), 5.14 (2H, s), 5.45 (1H, bs, -OH), 5.87 (2H, s, -O-CH_2-O-), 6.40 (1H, d, J=3.5Hz), 6.50-6.70 (4H, m, aromatic), 6.96 (1H, d, J=3.5Hz), 7.16 (1H, s); m/e 297 (M^+), 178 (4), 148 (6), 135 (100).

3-Veratrylidene-5, 6-dimethoxyoxindole (26)[13]

5, 6-Dimethoxyoxindole (10g, 0.052mol) and veratraldehyde (10.8g, 0.065mol) with a few drops of piperidine were heated under reflux in dry toluene 150 cm^3 for 3 hours using a constant water separator. Evaporation of the solvents gave red crystals (12.6g, 71%), m.p. 201-202°C (ethanol, lit[13]., 200°0), ν max 3160, 1689, 1630, 1610cm^{-1}.

<u>3-Veratryl-5, 6-dimethoxyoxindole</u> (25)[13]

The foregoing compound (8g, 0.023mol) was dissolved in acetic acid (250cm^3) and hydrogenated for 4 hours at 40°C in the presence of Adam's catalyst. Evaporation of the solvent gave the title compound in almost quantitative yield (7.8g, 97%), m.p. 128-129°C (ethanol, lit[13]., 128°C), ν max 3140, 1700, 1628, 1604cm^{-1}; δ ($CDCl_3$) 2.80 (1H, m, diasterioso-topic), 3.41 (1H, m), 3.65 (3H, s, OMe), 3.75 (3H, s, OMe), 3.78 (1H, m), 3.80 (6H, s, 2 x OMe), 6.34 (1H, s), 6.53 (1H, s), 6.70-6.80 (3H, m), 9.32 br (1H, s); <u>m/e</u> 343 (M^+).

<u>3-Hydroxy-5, 6-dimethoxy-3(3, 4-dimethoxybenzyl) indolin-2 (3H)-one</u> (27)

The oxindole (25) (1.5g) was electrolysed in the usual manner until 1F mol^{-1} of current had been consumed. Work-up of the anolyte gave an oil which slowly crystallized to give prisms (0.44g, 28%), m.p. 175-176°C; ν max 3350 (weak), 3310, 1710, 1690, 1670cm^{-1}; δ ($CDCl_3$) 2.80 (1H, s, OH), 3.36 (1H, d, <u>J</u>=13Hz), 3.54 (3H, s, OMe), 3.75 (9H, s, 3 x OMe), 4.10 (1H, d, <u>J</u>=13Hz), 6.25 (1H, s), 6.38 (1H, s), 6.50-6.60 (3H, m), 9.06 (1H, s, -NH); <u>m/e</u> 359 (M^+), 343 (15), 341 (33), (Found: C, 63.6; H, 6.0; N, 3.9 $C_{19}H_{21}NO_6$ requires C, 63.5; H, 5.8; N, 3.9%).

<u>3-Hydroxy-5, 6-dimethoxy-3-(4', 5'-dimethoxybenzyl)-2' {3-(5, 6-dimethoxy-3-(3, 4-dimethoxybenzyl) indolin-2 (3H)onyl)}</u>

The mother liquors from the foregoing experiment were evaporated and subjected to column chromatography (SiO_2, ethyl acetate/pet. ether) which gave colourless prisms (0.06g), m.p. 271-275°C (ethanol); ν max 3500, 3350, 3160, 1700, 1622 (weak), 1610, cm^{-1}; δ ($CDCl_3$) 1.63 (1H, s, -OH), 2.80 (1H, d, J=16Hz), 3.26 (2H, s), 3.66 (1H, d, J=16Hz), 3.72 (12H, s, 4 x OMe), 3.89 (12H, s, 4 x OMe), 6.00-6.60 (6H, m, aromatic), 6.65 (1H, s), 6.76 (1H, s), 7.12 (1H, s, -NH), 7.41 (1H, s), 7.53 (1H, s, -NH); m/e 682 (M^{+}-18), 531 (20), 341 (100).

<u>1-Acetyl-3-veratryl-5, 6-dimethoxyindolin-2-one</u> (30)

The oxindole (25) (4.0g, 0.011mol) was heated under reflux in a solution of acetic anhydride (25cm^3) and acetic acid (2.5cm^3) for 6 hours. Evaporation of the solvents gave a pale green oil, which triturated with ether (4.3g, 97%), m.p. 104-105°C (ethanol); ν max 1750, 1700, 1600cm^{-1}, δ ($CDCl_3$) 2.60 (3H, s), 2.88 ($\frac{1}{3}$H, d, J=15Hz), 2.96 ($\frac{2}{3}$H, d, J=15Hz), 3.38 ($\frac{1}{3}$H, d, J=15Hz), 3.43 ($\frac{2}{3}$H, d, J=15Hz), 3.70-3.92 (12H, 4 x s, 4 x OMe), 6.40 (1H, s), 6.61 (1H, s), 6.64-6.76 (3H, m), 7.90 (1H, s); m/e 385 (M^+), 235, 192, 151.

<u>9, 10-Dihydro-3, 6, 7-trimethoxy-4α, 10-iminomethanophenanthrene-2, 11-dione</u> (31)

The foregoing compound (1.0g, 0.0026mol) was electrolysed in the presence of anhydrous potassium carbonate. A high current density was necessary to maintain the electrode potential at 1.05v. Work-up of the anolyte was followed by column chromatography (alumina, chloroform) which afforded colourless prisms (0.13g, 15%), m.p. 286-288°C (ethanol); λ max 212, 245, 270 nm; ν max 3310, 1740, 1650, 1635, 1610cm^{-1}; δ ($CDCl_3$) 3.40 (3H, bs, CH_2OH), 3.65, 3.80 and 3.90 (each 3H, s, OMe) and 5.8, 5.95, 6.50 and 6.87 (each 1H, s, olefinic or aromatic): m/e 327 (M^+); (Found: C, 65.9; H, 5.1, N, 4.4 $C_{18}H_{17}NO_5$

requires C, 66.0; H, 5.2; N, 4.3%).

10, 15-Dihydro-2, 3, 7, 8, 12, 13 trimethoxytriethoxy-5H-tribenzo [a, d, g] cyclononene (35)[33]

3-Ethoxy-4-methoxybenzyl chloride (10g, 0.05mol) together with sodium cyanide (3.6g, 0.075mol) and sodium iodide (0.5g, 0.003mol) were heated under reflux in dry acetone for 2 hours. The solution was poured into water ($200cm^3$) and extracted with dichloromethane (3 x 50ml). The combined extracts were dried ($MgSO_4$), and evaporated to give an oil which slowly crystallized to give prisms (1.7g, 21%), m.p. 173-175°C; ν max 1608, $1591cm^{-1}$; δ ($CDCl_3$) 1.24 (9H, t, _J_=6Hz), 3.48 (3H, d, _J_=14Hz), 3.70 (9H, s), 3.86-4.18 (6H, m), 4.68 (3H, d, _J_=14Hz), 7.05 (6H, s); _m/e_ 392 (M^+); (Found: C, 73.1; H, 7.6 $C_{30}H_{36}O_6$ requires C, 73.1; H, 7.4%).

5, 6-Dimethoxyindoline

5, 6-Dimethoxyoxindole (7g, 0.036mol) was heated under reflux in tetrahydrofuran containing diborane (1M, $108cm^3$) for 1 hour. The solution was cooled and poured into hydrochloric acid (1.0M, $100cm^3$) and stirred for 1 hour. The mixture was extracted with dichloromethane, basified with sodium hydroxide and re-extracted with dichloromethane. Evaporation of the extracts of the basified solution gave an oil which triturated with ether (1.4g, 22%), m.p. 82-85°C (triturated from ether); ν max 3340, 1615, $1505cm^{-1}$; δ($CDCl_3$) 3.04 (2H, t, _J_=6Hz), 3.62 (2H, t, _J_=6Hz), 3.93 (6H, s, 2 x OMe), 6.41 (1H, s), 6.83 (1H, s); _m/e_ 179 (M^+).

<u>1-Homoveratroyl-5, 6-dimethoxyindoline</u> (36)

Homoveratric acid chloride (1.68g, 0.0078mol) and 5, 6-dimethoxyindoline (1.40g, 0.0078mol) were heated under reflux in a solution of benzene (25cm^3) and pyridine (3cm^3). The solution was cooled and extracted with water (2.100ml) and evaporated to give an oil which slowly crystallized (1.9g, 68%), m.p. 122-124°C (ethanol); ν max 1630, 1600, 1589cm^{-1}; δ ($CDCl_3$) 2.95 (2H, t, <u>J</u>=8Hz), 3.70 br (14H, s, 4 x OMe + Ar-CH_2-CO), 4.12 (2H, t, <u>J</u>=8Hz), 6.70-6.92 (4H, m, aromatic), 7.91 (1H, s); <u>m/e</u> 357 (M^+), 179 (90), 164 (80), 151 (87).

<u>3-Homoveratroylindole</u> (40)

Homoveratroyl chloride (18g, 0.084mol) was dissolved in anhydrous ether (75cm^3) and the solution was cooled in an ice bath. An ice cold solution of indole magnesium bromide (0.08mol) in ether (100cm^3) and dichloromethane (25cm^3) was added slowly to the solution of the acid chloride maintaining the temperature below 5°C. The solution was stirred for 2 hours and allowed to stand at room temperature overnight. The organometallic complex was hydrolysed with a saturated solution of ammonium chloride (200cm^3) and extracted with dichloromethane. Evaporation of the organic extracts gave a powder (16.3g, 66%). m.p. 174-176°C; ν max 3410, 3150, 1630, 1500cm^{-1}; <u>m/e</u> 295 (M^+).

<u>3- [α-Hydroxy-β-(3, 4-dimethoxyphenyl)ethyl] indole</u> (41)

The foregoing compound (5g, 0.017mol) was stirred in ethanol (40cm^3) containing sodium borohydride (2g) at 40°C until no further change in the u.v. spectrum was observed.

Excess reagent was destroyed by the addition of acetone and the solution was poured into water ($200cm^3$) and extracted with dichloromethane. Evaporation of the organic extracts gave an oil which crystallized to give prisms (4.3g, 87%), m.p. 149-150°C (ethanol); ν max 3560, 3380, 1600, $1520cm^{-1}$; δ ($CDCl_3$) 2.16 (1H, s, OH), 3.16 (2H, d, J 7Hz), 3.68 x 3.79 (each 3H, s, 2 x OMe), 5.16 (1H, t, J=7Hz), 6.63 (1H, s), 6.74 (2H, s), 6.92 (1H, d, J=3.5Hz), 7.0-7.32 (3H, m), 7.68-7.80 (1H, m), 8.30 br (1H, s, NH); m/e 297 (M^+).

3-[β-(3, 4-Dimethoxyphenyl)ethyl] indole (39)

The indole (40) (7g, 0.023mol) was heated under reflux in a solution of n-propanol ($50cm^3$) containing sodium borohydride (3g) for ½ hour. Excess reagent was destroyed by dilute mineral acid and the solution was partitioned between dichloromethane/water. The organic layer was separated and evaporated to give a powder (5.2g, 79%), m.p. 114°C; λ max 223, 283, 335 nm; ν max 3380, 1597, $1580cm^{-1}$; δ ($CDCl_3$) 2.96 (4H, bs, $-CH_2-CH_2$), 3.73 x 3.79 (each 3H, s, 2 x OMe), 6.60-6.80 (3H, m, aromatic), 6.95-7.25 (4H, m), 7.46-7.60 (1H, m), 7.86 (1H, bs); m/e 281 (M^+), 151, 130, 117.

1-Acetyl-3-[β-(3, 4-dimethoxyphenyl)ethyl] indole (42)

The foregoing indole (5.0g, 0.017mol), was heated under reflux in a solution of acetic anhydride ($25cm^3$) and acetic acid ($2.5cm^3$) for 12 hours. Evaporation of the solvents gave an oil which triturated with ether to give a pale green powder (5.0g, 87%), m.p. 108-110°C; λ max 209, 229, 275, 302 nm; ν max 1700, 1604, $1592cm^{-1}$; δ ($CDCl_3$) 2.52 (3H, s), 2.92 (4H, bs, $-CH_2-CH_2-$) 3.81 (6H, s, 2 x OMe), 6.71 (3H, m), 7.07 (1H, s), 7.20-7.55 (4H, m); m/e 323 (M^+), 287, 172, 151.

3-[3-(3, 4-Dimethoxyphenyl)propyl-1-one] indole (44)

The experimental procedure used for the synthesis of this compound was identical to that used for the preparation of (40). Thus the reaction between β-(3, 4-dimethoxyphenyl)propionoyl chloride (12g, 0.052mol) and indole magnesium bromide (0.05mol) gave on work-up, a colourless powder (10.2g, 64%), m.p. 137-138°C (methanol); λ max 215, 217, 240, 263, 283, 287 nm; ν max 3200, 1630, 1615cm^{-1}; δ ($CDCl_3$ + d^6 DMSO) 2.90 (2H, t, J=6.5Hz), 3.12 (2H, t, J=6.5Hz), 3.70 (6H, s, 2 x OMe), 6.75-6.92 (3H, m), 7.10-7.52 (3H, m), 8.15-8.34 (2H, m); m/e 309 (M^+), 165 (25), 164 (45), 151 (43), 144 (100).

Indolo[2, 3b] bicyclo[5, 4, 0] undec-1, 7, 11-trien-4, 9, 10-trione (45)

The previous compound (1.0g, 0.0032mol) was electrolysed at an electrode potential of 1.25v until 2F mol^{-1} of current had been consumed. Work-up of the anolyte gave a dark solid which yielded a black powder from column chromatography (SiO_2, ethyl acetate, pet. ether). The product was photo-sensitive, and therefore the whole work-up procedure was conducted under minimal light conditions, (0.06g, 7%), m.p. 220-240°C; λ max 215, 241, 310, 350nm; νmax 3340, 1670, 1658, 1640 , 1630, 1615, 1530cm^{-1}; δ ($CDCl_3$) 2.95 (4H, s, $-CH_2-CH_2$), 6.56 (1H, s), 6.80 (1H, s), 7.25-7.72 (3H, m, aromatic), 8.00 (1H, d, J=8Hz), 12.60 br (1H, s, NH); m/e 277 (M^+). (Found: C, 73.5; H, 3.6; N, 5.0 $C_{17}H_{11}NO_3$ requires: C, 73.6; H, 4.0; N, 5.05%).

<u>6, 7-Dimethoxy-3-isochromanone</u> (58)[49]

A solution of homoveratric acid (23.4g, 0.12mol) in glacial acetic acid (60cm^3) was mixed with concentrated hydrochloric acid (20cm^3) and formalin solution (37%, 20cm^3) and heated on a steam bath for 1 hour. The solution was cooled and poured into cold water (600cm^3) and extracted with chloroform. The organic extracts were washed with sodium carbonate solution (5%) and evaporated to give an oil which was triturated with ether to give a colourless powder (19.1g, 77%), m.p. 107-108^{o}C (ethanol, lit[49]., 108-109.5^{o}C), ν max 3520, 1725, 1610cm^{-1}; δ ($CDCl_3$) 3.61 (2H, s), 3.88 (6H, s, 2 x OMe), 5.26 (2H, s), 6.72 (2H, s, aromatic); <u>m/e</u> 208 (M^+).

<u>Ethyl 2-bromomethyl-4, 5-dimethoxyphenylacetate</u> (59)

To a solution of dry hydrogen bromide (20g)in anhydrous ethanol (300cm^3) was added 6, 7-dimethoxy-3-isochromanone (5.0g, 0.024mol). The solution was stirred for 24 hours and the solvent evaporated at 20^{o}C (3-5mm) to give a colourless oil which triturated with ether (7.0g, 93%), m.p. 55-57^{o}C; ν max 1717, 1602cm^{-1}; δ ($CDCl_3$) 1.25 (3H, t, <u>J</u>=7Hz), 3.70 (2H, s), 3.86 (6H, s, 2 x OMe), 4.16 (2H, q, <u>J</u>=7Hz), 6.78 (1H, s), 6.88 (1H, s); <u>m/e</u> 318 and 316 (M^+), 238 (100), 192 (30).

<u>1, 4-Dihydro-6, 7-dimethoxy-2-methyl-3(2H)-isoquinolone</u> (56)[49]

The previous compound (2g, 0.0063mol) in dry ether (50cm^3) and methylamine solution (33%, 1.2g, 0.012mol) was heated in a stainless steel bomb (capacity, 60cm^3) at 100^{o}C for 2 hours. The solution was extracted with water (2 x 25cm^3) and evaporated to give an oil which promptly solidified, to give pale yellow crystals (1.0g, 70%), m.p. 118-119^{o}C (lit[49]., 119.5-121.5°C), ν max 1630, 1600cm^{-1}; δ ($CDCl_3$) 3.22 (3H, s), 3.70 (2H, s), 4.00 (6H, s), 4.60 (2H, s), 6.80 (2H, s), m/e 221 (M^+), 206 (20), 192 (30), 164 (100).

<u>4-Ethyl-6, 7-dimethoxy-2-methyl-3(2H)-isoquinolone</u> (62)

N-Butyl-lithium in tetrahydrofuran (1.0m, 3.6cm^3) was stirred with diisopropylamine (0.36g, 0.0036mol) in dry tetrahydrofuran (5cm^3) at room temperature for 1 hour. To this solution, was added the isoquinolone (56) (0.4g, 0.0018mol) in tetrahydrofuran (5cm^3) and the resulting mixture stirred at room temperature. After 2 hours methyl iodide (0.51g, 0.0036mol) was added dropwise and the solution stirred for a further 3 hours, and poured into water (100cm^3). Extraction of the aqueous solution with dichloromethane and evaporation of the organic extracts gave a pale yellow oil (0.37g, 83%), ν max 1640 (br), 1522cm^{-1}; δ ($CDCl_3$) 0.62 and 0.80 (3H, 2 x t, J=10Hz, 2:1), 1.20-2.50 (2H, m, -$\underline{CH_2}$-CH_3), 3.09 and 3.14 (3H, 2 x s, 1:2, N-Me), 3.85 (6H, bs, 2 x OMe), 4.50 (2H, s), 6.58 (1H, s), 6.68 (1H, s); m/e 249 (M^+).

<u>3-Veratrylidene-6, 7-dimethoxy-3-isochromanone</u> (63)

6, 7-Dimethoxy-3-isochromanone (5g, 0.024mol) and veratraldehyde (4.0g, 0.024mol) were heated together on a steam bath in the presence of pyrrolidine (1cm^3) for 30 minutes. The mixture was cooled and triturated with ether to give pale yellow prisms (7.5g, 86%), m.p. 176-178°C; ν max 1723, 1605, 1520cm^{-1}.

<u>3-Veratryl-6, 7-dimethoxy-3-isochromanone</u>

The foregoing compound (5.0g, 0.014mol) was dissolved in ethanol ($250cm^3$) and shaken under hydrogen (60 p.s.i.) for 5 hours in the presence of Adams catalyst. The resulting solution was filtered and evaporated to give colourless prisms (4.7g, 94%), m.p. 83-84°C; ν max 1722, 1608, $1590cm^{-1}$; δ ($CDCl_3$) 3.16 (2H, d, *J*=7Hz), 3.68, 3.76, 3.83, 3.85 (12H, 4 x s, 4 x OMe), 3.79 (1H, q, *J*=7Hz), 4.55 (1H, d, *J*=15Hz), 4.96 (1H, d, *J*=15Hz), 6.36-6.78 (5H, m, aromatic), *m/e* 358 (M^+), 208 (35), 164 (30), 151 (100).

<u>Ethyl 1-(3, 4-dimethoxybenzyl)-2-bromomethyl-4, 5-dimethoxyphenylacetate</u> (64)

The compound from the previous experiment (1.0g, 0.0028mol) was stirred in a solution of ethanol ($50cm^3$) containing dry hydrogen bromide (5g) at room temperature for 24 hours. Evaporation of the solvents at 20°C under reduced pressure gave a colourless oil which slowly crystallized to give colourless photosensitive crystals (1.05g, 81%), m.p. 84°C; ν max 1725, 1600, $1583cm^{-1}$; δ ($CDCl_3$) 1.10 (3H, t, *J*=6Hz), 2.8-3.6 (2H, m), 3.80-3.85 (12H, 3s, 4 x OMe), 3.85-4.8 (5H, m), 6.78 (4H, s), 7.02 (1H, s); *m/e* 468 and 466 (M^+).

Experimental for Chapter 3

Veratrylhomoveratrate (3)

Veratryl alcohol (5.0g, 0.03mol) and homoveratroyl chloride (6.4g, 0.03mol) were heated under reflux in a solution of dry benzene ($50cm^3$) and pyridine ($4.5cm^3$, 0.06mol) for 1 hour. The solution was cooled, washed with hydrochloric acid (0.1M) and then with saturated sodium carbonate solution and finally evaporated to give an oil which when triturated with ether gave a colourless powder. (7.8g, 76%), m.p. 125°C; δ ($CDCl_3$) 3.54 (2H, s), 3.91 (12H, bs, 4 x OMe), 4.80 (2H, s), 6.75-6.90 (6H, m, aromatic); m/e 346 (M^+).

'Uncontrolled' potential oxidation of N, N-dibenzylacetamide (8)

The experimental conditions employed for this oxidation are the same as those described previously (page 189). The electrolysis of N, N-dibenzylacetamide (1.5g) in acetonitrile proceeded with an initial electrode potential of 1.90v, but this potential rose and stabilized at 2.30v (*vs* SCE). The oxidation was discontinued after 2F mol^{-1} of current had been consumed and the crude oil obtained from work-up of the anolyte was subjected to column chromatography (SiO_2, $CHCl_3$/EtOH 9:1) to remove any slow running resinous components before GLC analysis. The GLC analysis was conducted using two columns, 2.5% OV1 on chromasorb W and 15% Apiezon L on universal B; retention times for various flow rates and temperatures are already detailed in the discussion.

Homoveratrylhomoveratrate (9)

The title compound was prepared in the same manner to that of the ester (3) and was isolated as a pale orange oil

(73%), ν max 1725, 1600, 1590cm^{-1}; δ ($CDCl_3$) 2.87 (2H, t, J=7Hz), 3.56 (2H, s), 3.86 (12H, bs, 4 x OMe), 4.30 (2H, t, J=7Hz), 6.72-6.85 (6H, m, aromatic); m/e 360 (M^+), 196 (60), 164 (90), 151 (90).

Electrolysis of homoveratrylhomoveratrate

The foregoing compound (1.5g) was electrolysed in the usual manner at an electrode potential of 1.10v (vs SCE) until 2F mol of current had passed. The oil obtained after work-up, was subjected to column chromatography (SiO_2 ethylacetate/pet. ether) which gave two major fractions.

1st Fraction - this fraction yielded a polymeric compound based upon structure (11), obtained as an amorphous orange solid (0.3g), m.p. 60-95°C; ν max 1725, 1600, 1585cm^{-1}; δ ($CDCl_3$) 2.61 (2H, m), 3.26 br (2H, s), 3.85 br (12H, s, 4 x OMe), 4.08 (2H, m), 6.60-6.82 (4H, m, aromatic); m/e ca. 1080 (M^+), 720 (M^+), (L. eV).

2nd Fraction - this consisted of 'dimeric' species with structures similar to (10); obtained as a pale orange amorphous solid (0.7g) m.p. 75-90°C; ν max 1725, 1600cm^{-1}; δ ($CDCl_3$) 2.65 (2H, t, J=6.5Hz), 3.34-3.52 (2H, m), 3.80 (12H, bs, 4 x OMe), 4.25 (2H, t, J=6.5Hz), 6.50-6.90 (4H, m, aromatic); m/e ca. 716 (M^+).

Bis-1, 3-(3, 4-dimethoxyphenyl)-2-propanone (12)

Dry tetrahydrofuran (30cm^3) was added to a mixture of N, N′-carbonyl diimidazole (8.2g, 0.051mol) and homoveratric acid (10g, 0.051mol). After the vigorous evolution of carbon dioxide had subsided the solution was degassed with dry nitrogen for 30 minutes. The solution was cooled to -10°C and lithium aluminium hydride (0.5g, 0.013mol) was added in 0.1g portions and the temperature allowed to rise to 20°C over 3 hours. Excess tetrahydrofuran was distilled off, and the oil separated between chloroform/water. The organic extract was washed with water and evaporated to give an oil which crystallized overnight to give prisms (3.6g, 43%), m.p. 103-105°C (ethanol) (lit[19]., 84-86°C); ν max 1707, 1604, 1590cm^{-1}; δ ($CDCl_3$) 3.64 (4H, s), 3.82 (12H, bs, 4 x OMe), 6.75-6.84 (6H, m, aromatic); m/e 330 (M^+).

<u>2, 3, 9, 10-Tetramethoxydibenzo [a, c] cycloheptadien-6-one</u> (13)

The foregoing compound (1.50g) was electrolysed at an electrode potential of 1.15v (vs SCE) until 2F mol^{-1} of current had been utilized. Work-up in the usual manner gave a viscous oil which triturated with ethanol, to give colourless prisms (0.67g, 45%), m.p. 230-240°C (dec.) (lit[20]., 259°C), ν max 1705, 1600, 1585cm^{-1}; δ ($CDCl_3$) 3.52 (4H, s), 4.03 (12H, bs, 4 x OMe), 6.80 (2H, s), 7.10 (2H, s); m/e 328 (M^+), 300 (10), 285 (15), 151 (100). (Found: C, 69.4; H, 6.1 calc. for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1%).

<u>4-Methoxybenzyl 1-(4-methoxyphenyl)acetate</u> (15)

The title compound was prepared by the combination of the respective acid chloride and alcohol by the general method outlined for ester (3), to give a colourless powder (61%), m.p. 67-69°C; ν max 1722, 1617, 1590cm^{-1}; (Found: C, 71.3; H, 6.2 calc. for $C_{17}H_{18}O_4$: C, 71.2; H, 6.0%).

4-Methoxyphenyl 1-(4-methoxyphenyl)acetate (16)

This compound was prepared by a similar method to that described for the preparation of ester (3), (63%), m.p. 73-75°C; ν max 1740, 1615, 1600cm^{-1}; δ ($CDCl_3$) 3.85 br (8H, s, 2 x OMe, $-CH_2-$), 6.70-7.45 (8H, m, aromatic).

4-Methoxyphenyl 3-methoxybenzoate (17)

The title compound was obtained by the standard procedure as colourless prisms (73%), m.p. 64-65°C (ether), ν max 1720, 1600cm^{-1}; δ ($CDCl_3$) 3.81 (3H, s, OMe), 3.89 (3H, s, OMe), 6.80-7.40 (8H, m, aromatic); m/e 258 (M^+).

2, 2′-Dimethoxy-5, 5′-bis-(3-methoxybenzoyloxy)biphenyl (21)

The foregoing compound (1.0g) was oxidized in the usual way at an anode potential of + 1.4v, the cell current being maintained at ca 50 mA (1F mol^{-1} current utilization). Column chromatography on silica gel (elution with 20% ethyl acetate in petroleum (b.p. 60-80°C)) gave the diester (21) as a pale yellow crystalline solid (0.64g, 65%); m.p. 113-114°C; m/e 514 (M^+); λ max 224 (ϵ 31,400), 241 (28,400) and 292 (15,500); ν max 1732, 1601, 1590cm^{-1}; δ ($CDCl_3$) 3.72 (6H, s, 2 x OMe), 3.82 (6H, s, 2 x OMe), 6.90 br (2H, d, J=9Hz) 6.95-7.28 (6H, m), 7.38 (2H, t, J=7Hz), 7.69 br (2H, t, J=2Hz), 7.72 br (2H, dt, J=7 and 2 Hz); (Found: C, 70.0; H, 5.1 $C_{30}H_{26}O_8$ requires: C, 70.0; H, 5.1%).

3-(1, 4-Benzoquinon-2-yl)-4-methoxyphenyl 3-methoxybenzoate (22)

A repetition of the above experiment, but allowing 3F mol^{-1} equivalent of current to be utilized, gave on work-up a red oil. G.l.c. analysis (10% OV1 on Chromosorb W, AW/DCMS, at 237°C) showed two peaks, that of lower retention being due to 3-methoxybenzoic acid (identified by direct comparison and g.l.c. mass spectrometric studies with an authentic sample). The oil was chromatographed on silica gel (elution with ethyl acetate - petroleum (b.p. 60-80°C) mixtures). Initial fractions contained 3-methoxybenzoic acid and subsequent ones a red oil. After some weeks the oil slowly crystallised to afford the quinone (22) as yellow prisms (0.32g, 45%), m.p. 82-84°C; *m/e* 364 (M^+); λ max 241 (ε 19,400), 283 (8,200); ν max 1735, 1655, 1610, 1600cm^{-1}; δ ($CDCl_3$), 3.77 (3H, s, OMe), 3.82 (3H, s, OMe), 6.70-6.80 (3H, m, 1, 4-benzoquinonyl group), 6.88 (1H, d, $\underline{J}_{5^1,6^1}$=9Hz, H-5^1), 6.94 (1H, d, $\underline{J}_{2^1,6^1}$=2.5Hz, H-2^1), 7.04 (1H, dt, $\underline{J}_{4,5}$=7.5, $\underline{J}_{2,4}$=$\underline{J}_{4,6}$=1.7Hz, H-4), 7.15 (1H, dd, $\underline{J}_{5^1,6^1}$= 9Hz, $\underline{J}_{2^1,6^1}$=2.5Hz, H-6^1), 7.3 (1H, t, $\underline{J}_{4,5}$=$\underline{J}_{5,6}$=7.5Hz, H-5), 7.59 (1H, t, $\underline{J}_{2,4}$=$\underline{J}_{2,6}$=1.7Hz, H-2), 7.67 (1H, dt, $\underline{J}_{5,6}$ 7.5, $\underline{J}_{2,6}$=$\underline{J}_{4,6}$=1.7Hz, H-6), (Found: C, 69.2; H, 4.4. $C_{21}H_{16}O_6$ requires: C, 69.2; H, 4.4%).

<u>4-Methoxyphenyl benzoate</u> (26)

The title compound was obtained by the standard procedure as colourless prisms (86%), m.p. 56°C (ether), δ ($CDCl_3$) 3.86 (3H, s, OMe), 7.09-7.49 (7H, m, aromatic), 7.68 (1H, dd, $\underline{J}$=1.7Hz), 7.76 (1H, dd, J=7.5Hz, $\underline{J}_2$=1.7Hz); *m/e* 228 (M^+).

<u>5, 5′-Benzoyloxy-2, 2′-dimethoxybiphenyl</u> (27)

Oxidation of the foregoing compound as for its derivative (17) at an anode potential of +1.40v and an equivalent current utilization of 1F mol^{-1} gave the diester (27) as pale yellow prisms (70%), m.p. 161-163°C (ethyl acetate); λ max 241 (ε 17,400), 273 nm (9,800); ν max 1730, 1598, 1579cm^{-1};

δ ($CDCl_3$) 3.80 (6H, s, 2 x OMe), 6.90 (2H, d, J=9Hz), 7.10-7.30 (4H, m), 7.38-7.60 (6H, m), 8.08 (4H, dt, J=7 and 2Hz); m/e 454 (M^+); (Found: C, 74.0; H, 4.75. $C_{28}H_{22}O_6$ requires: C, 74.0; H, 4.9%).

3-(1, 4-Benzoquinon-2-yl)-4-methoxyphenyl benzoate (28)

This compound together with benzoic acid was obtained from the anodic oxidation of 4-methoxyphenyl benzoate at +1.40v after the equivalent of 3F mol^{-1} of current had been consumed. It was isolated as a yellow oil which failed to crystallize; λ max 241 (ε 23,000), 280 nm (7,770); ν max 1735, 1650, $1605cm^{-1}$; δ ($CDCl_3$) 3.80 (3H, s, OMe), 6.80-6.90 (3H, m), 7.00 (1H, d, $J_{5^1,6^1}$=9Hz, H-5^1), 7.11 (1H, d, $J_{2^1,6^1}$= 2.5Hz, H-2^1), 7.30 (1H, dd, $J_{5^1,6^1}$=9, $J_{2^1,6^1}$=2.5Hz, H-6^1), 7.50-7.65 (3H, m), 8.20 br (2H, dt, J=7Hz and 2Hz, H-2 and -6); m/e 334 (M^+); (Found: C, 71.8; H, 4.2. $C_{20}H_{14}O_5$ requires: C, 71.85; H, 4.2%).

3-(4-Methoxy-1, 2-benzoquinonyl)-4-methoxyphenyl benzoate (30) and 4-(3-Methoxy-1, 2-benzoquinonyl)-4-methoxyphenyl benzoate (32)

These compounds were obtained in late fractions 20% ethyl acetate in petroleum (b.p. 60-80°C) from chromatographic separation in the previous experiment. T.l.c. suggested the presence of a single compound, and the material crystallized as bright red prisms, m.p. 142-144°C; λ max 235 (ε 14500, 270 sh (10,000), 320 sh (3,100), 360 sh nm (1270); ν max 1730, 1680, 1669 sh, 1644, 1630, 1610 sh, $1596cm^{-1}$; δ ($CDCl_3$) 3.80 (3H, s, OMe), 3.88 (3H, s, OMe), 7.02 (1H, d, $J_{5^1,6^1}$=9Hz; H-5^1), 7.09 (1H, d, J=3Hz, H-2^1), 7.29 (1H, dd, $J_{5^1,6^1}$=9Hz;

$\underline{J}_{2^1,6^1}$=3Hz, H-6^1), 7.5-7.65 (3H, m), 8.20 br (2H, dt, $\underline{J}$ 7 and 2Hz, H-2 and -6^1). In addition were two doublets ($\underline{J}$=3.75Hz) at δ 5.98 and δ 6.80 and two singlets at δ 6.02 and δ 6.82. These signals which arise from the 1, 2-benzoquinonyl units present in structures (30) and (32) suggest that these compounds exist in the mixture in the ratio of 3:1. Attempts to separate these two components failed. $\underline{m/e}$ 364 (M^+), 258 (13%), 104 (50), 76 (100); (Found: C, 68.9; H, 4.1. $C_{21}H_{16}O_6$ requires: C, 69.2; H, 4.4%).

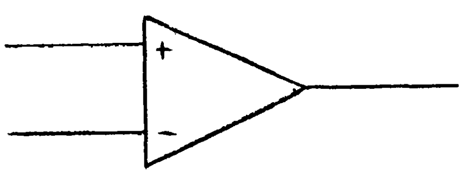
The construction of a Three Electrode Polarograph

When we first embarked upon the study of anodic oxidation, the only equipment at hand was a stabilized voltage source and high input impedance digital voltmeter. Although this equipment was adequate for conducting preliminary investigations, it soon became apparent that cyclic voltammetric equipment was necessary to elucidate the various electroorganic mechanisms involved in these reactions. The high cost of commercial equipment encouraged us to examine the possibility of building our own polarograph.

The advent of integrated circuit operational amplifiers has brought the building of electronic hardware for the laboratory into reach of the amateur. A brief description of the circuit is helpful to the understanding of some modifications that were necessary to obtain a versatile instrument.

The symbol for the operational amplifier (O.A.) is shown in Figure 1; the small signal inputs are connected to the (+) and (-) terminals and the output is indicated at the apex of the triangle.

Figure 1

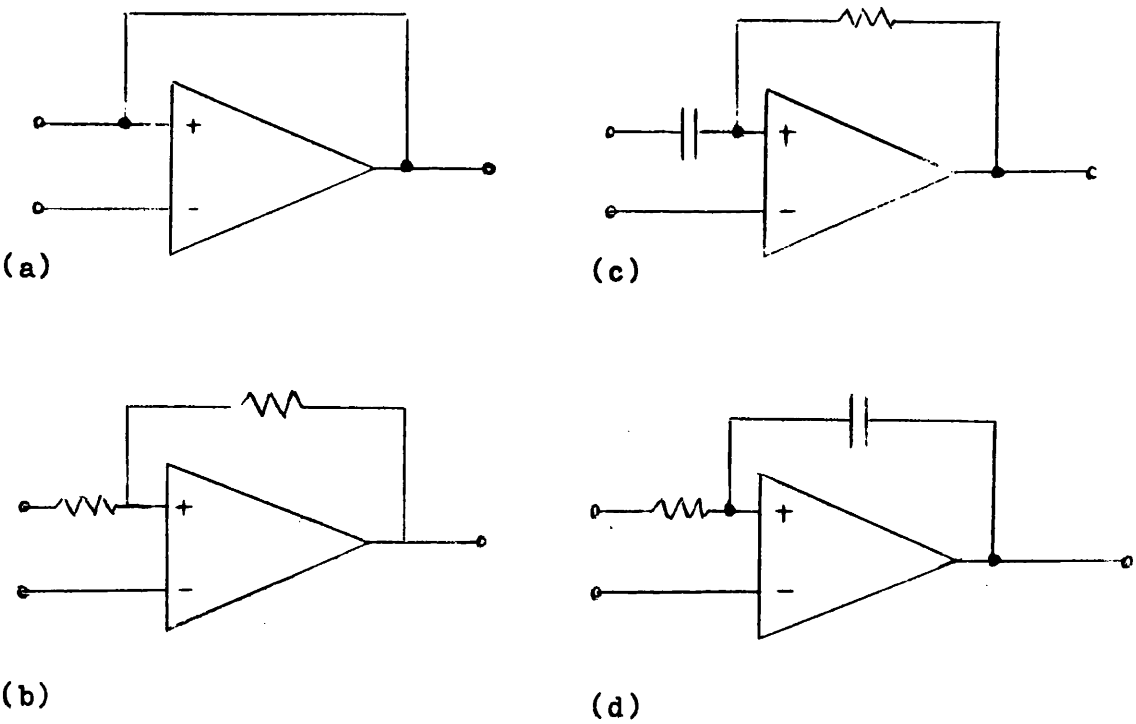


(+) non inverting input

(-) inverting input

With the minimum of external circuitry, an O.A. can function as a voltage follower, amplifier, differentiator or simple integrator; these four modes of operation being singled out because all the O.A.'s in the polarograph circuit (p.222)[1] fall into one of these four categories. Figure 2 shows the external circuiting necessary to make an O.A. function in one of these four modes.

Figure 2



V_I = voltage input V_O = voltage output

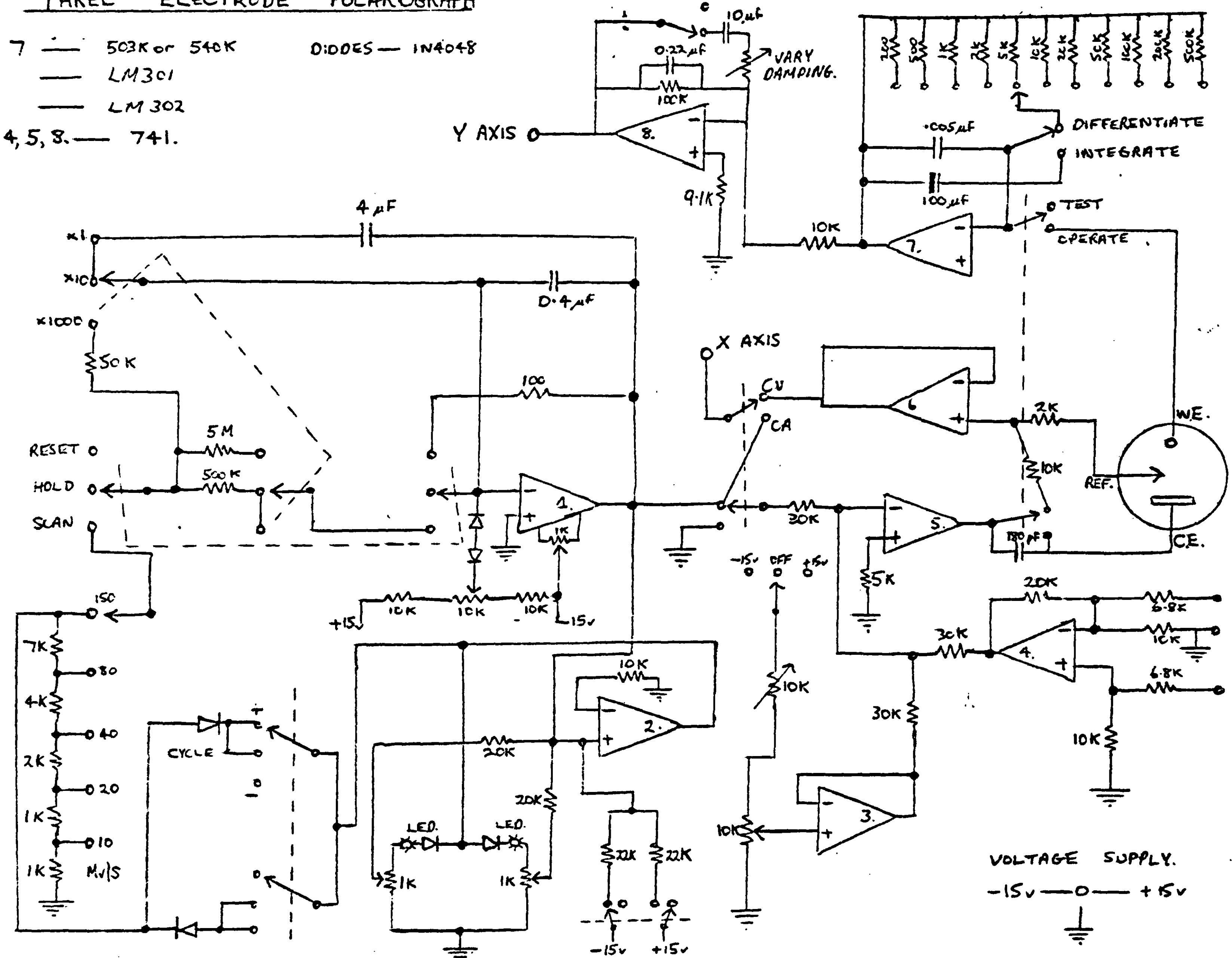
a. voltage follower c. differentiator

b. voltage amplifier d. integrator

THREE ELECTRODE POLAROGRAPH

1, 7 — 503K or 540K
2 — LM301
6 — LM302
3, 4, 5, 8. — 741.

DIODES — IN4048



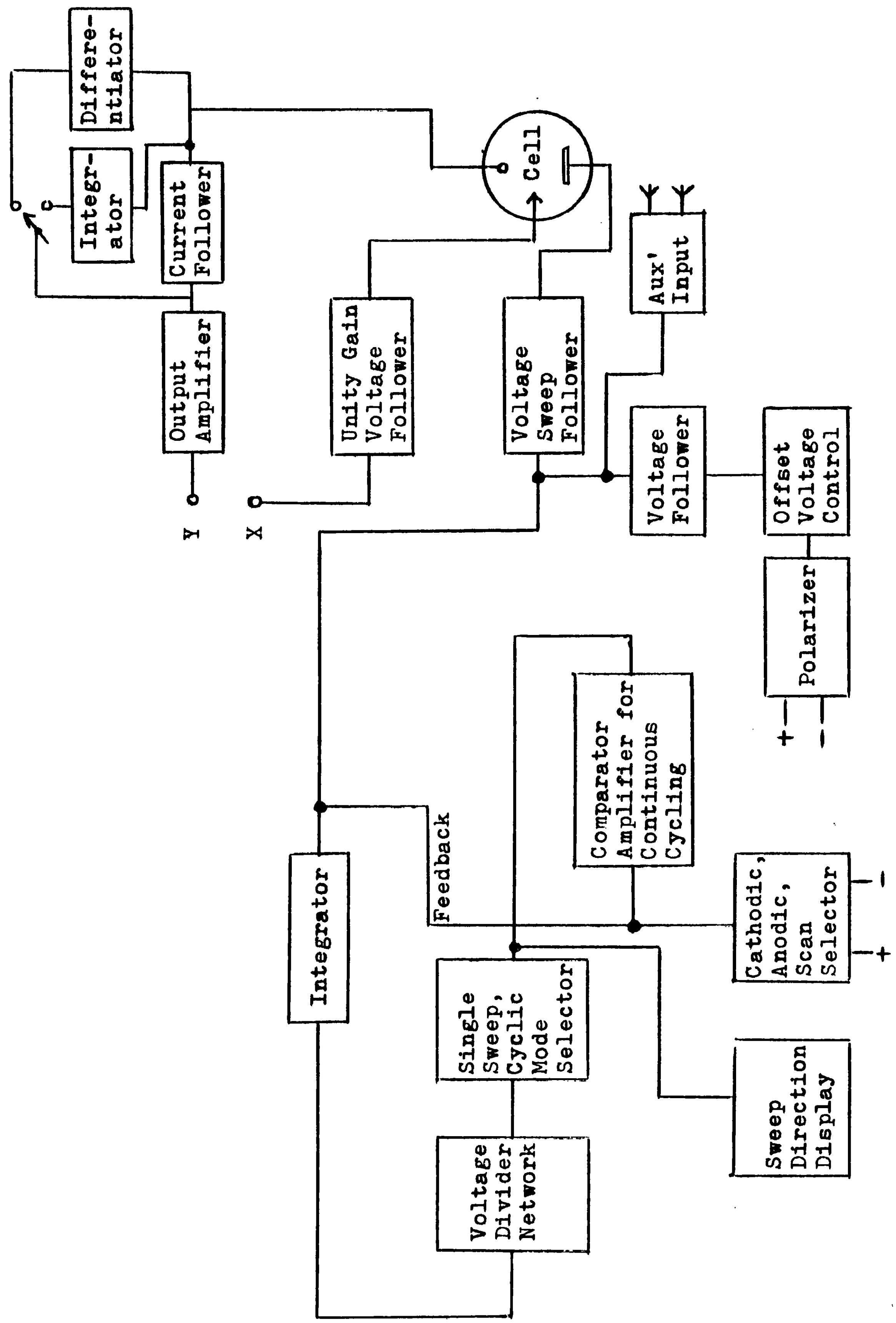
Analysis of the polarograph circuit (p. 222) with the aid of the above circuit elements, gives rise to the block diagram (p.224) which details the functioning of the complete unit.

Understanding the circuit operation was essential to make the simple alterations necessary to obtain satisfactory voltammetric data. For example, the O.A. (7) (p.222) in the original circuit supplied, operated in a differential mode i.e., it differentiated (with respect to time) the anode current. This is useful in providing highly resolved peaks and clearly defined peak potentials in the voltammogram, but is of little use when quantitative data relating to peak currents are required. Therefore, the addition of a switching system to allow the O.A. (7) to function as either a current differentiator or current follower was most useful.

The circuit layout was found not to be critical, as most of the O.A.'s function in either unity or low gain conditions, except for the comparator O.A. (2) which works at saturation point, and the current amplifier (7) which has variable gain.

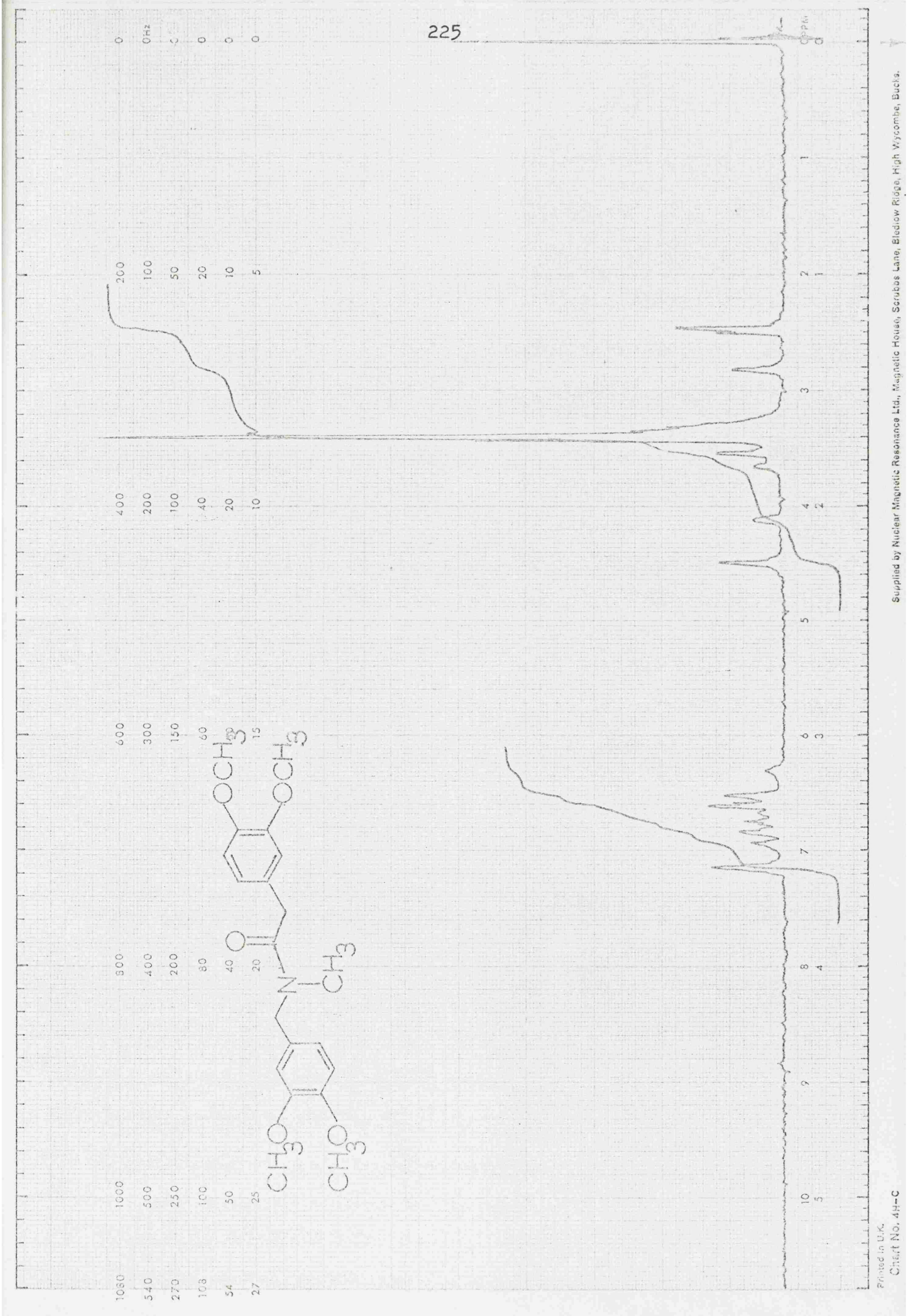
The complete unit was built for a fraction of the cost of a commercial equivalent, and its construction considerably aided the understanding of its operation.

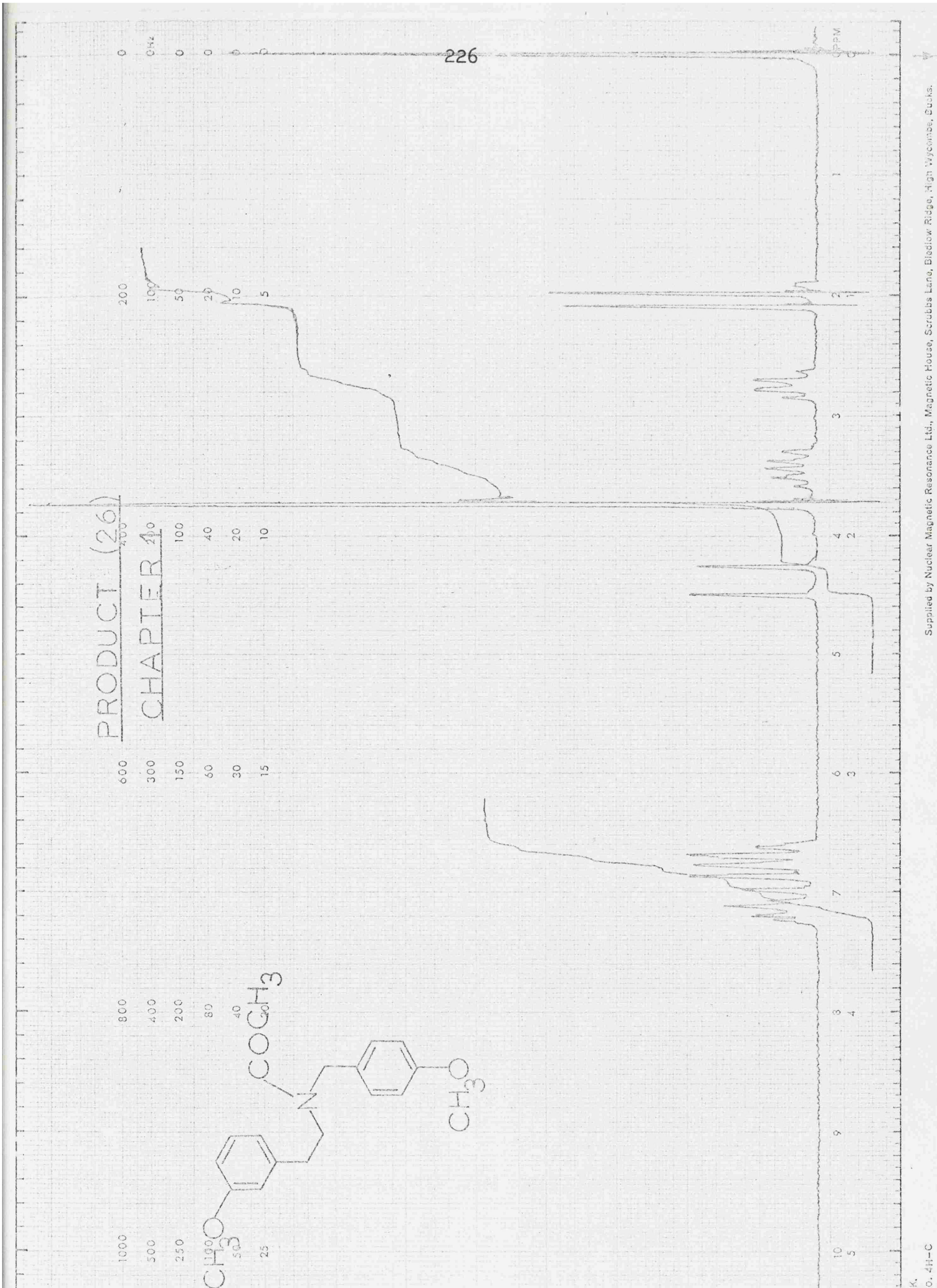
Block Diagram of the Three Electrode Polarograph



Spectra, Graph and Cyclic

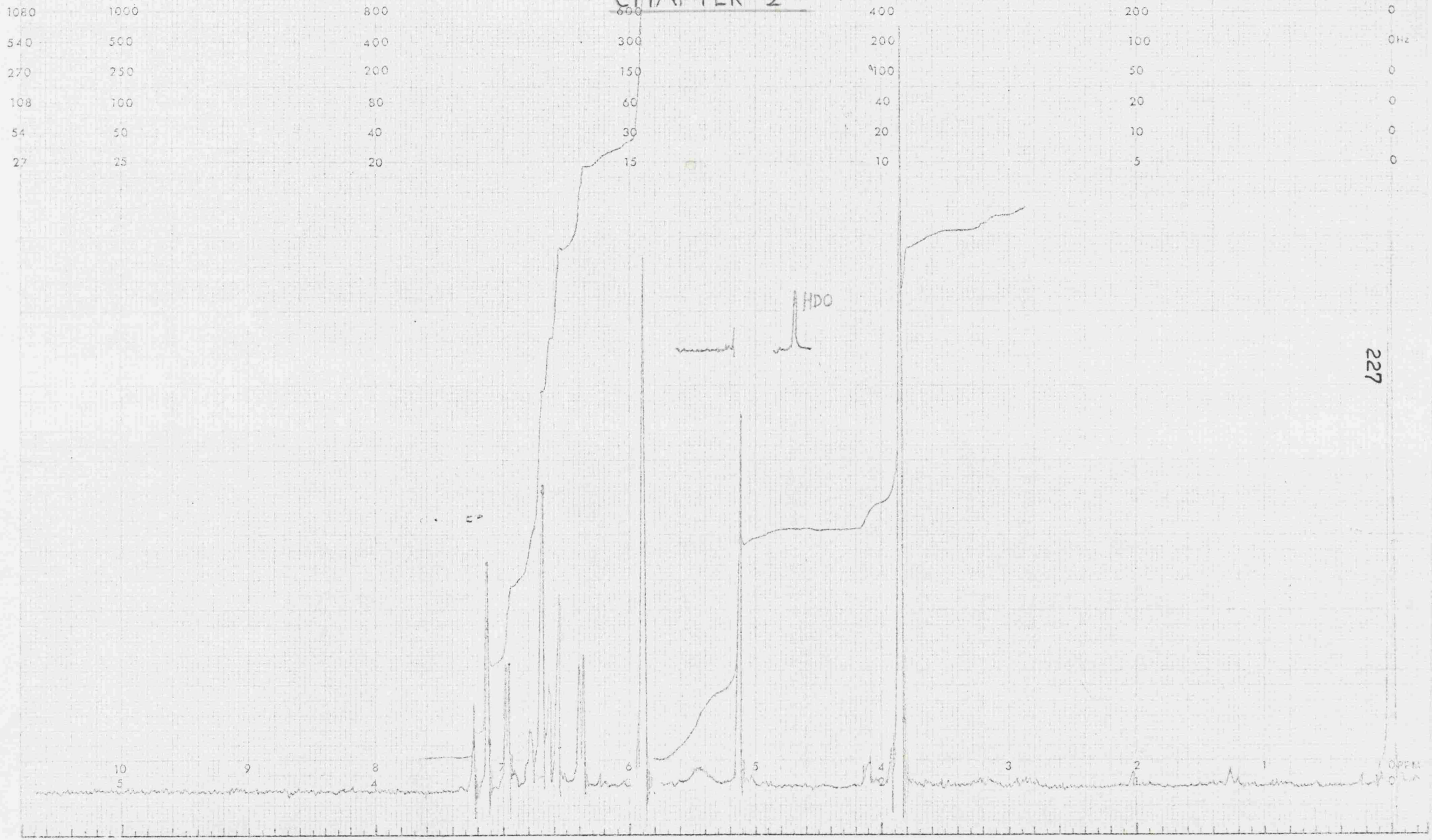
Voltammograms


Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.
Printed in U.K.
Chart No. 4H-C
PPM δ
0
1
2
3
4
5
6
7
8
9
10

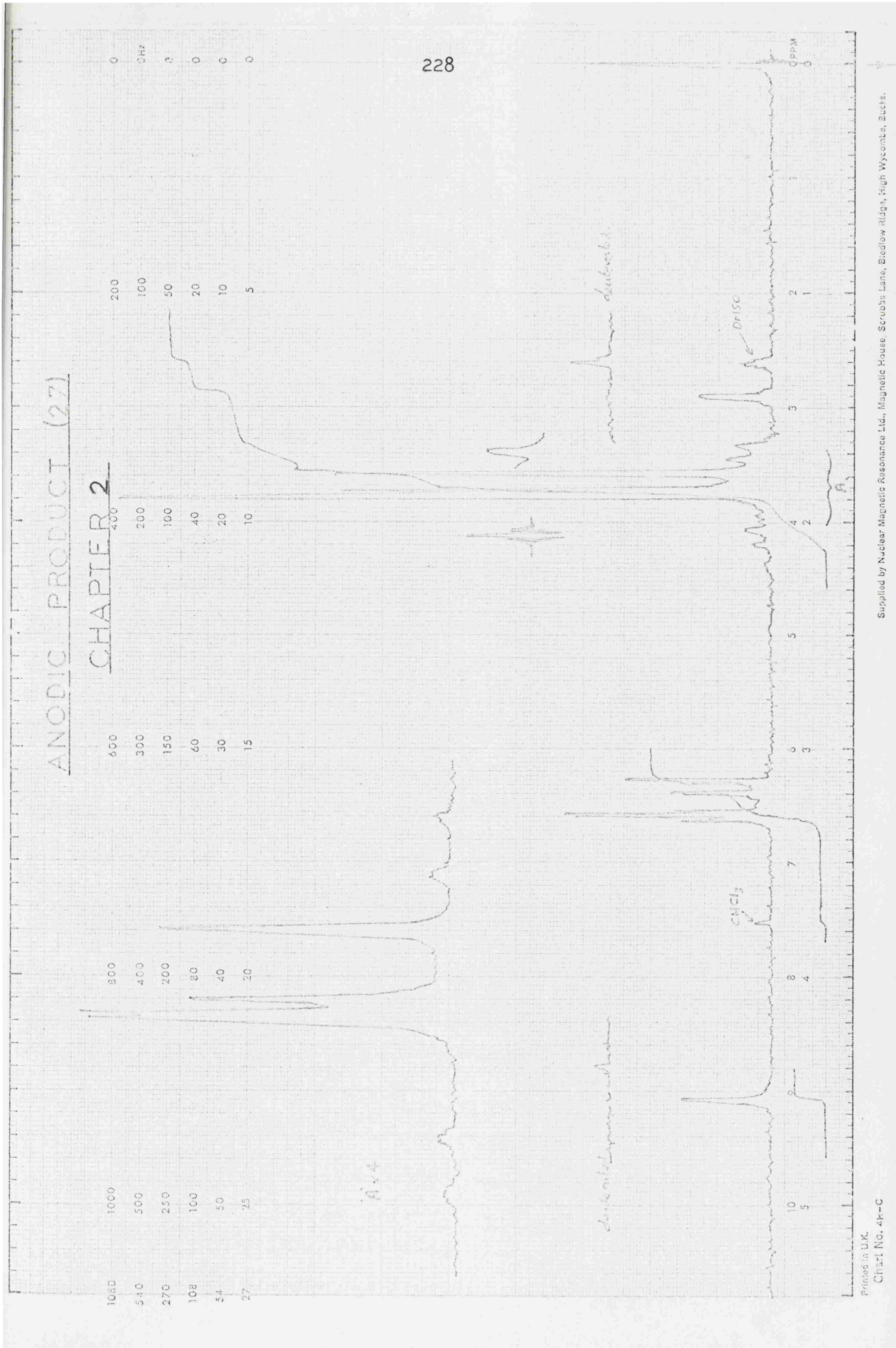

PRODUCT (26)
CHAPTER 4
COCH3
CH3O
CH3O
PPM
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.
Printed in U.K.
Chart No. 4H-C

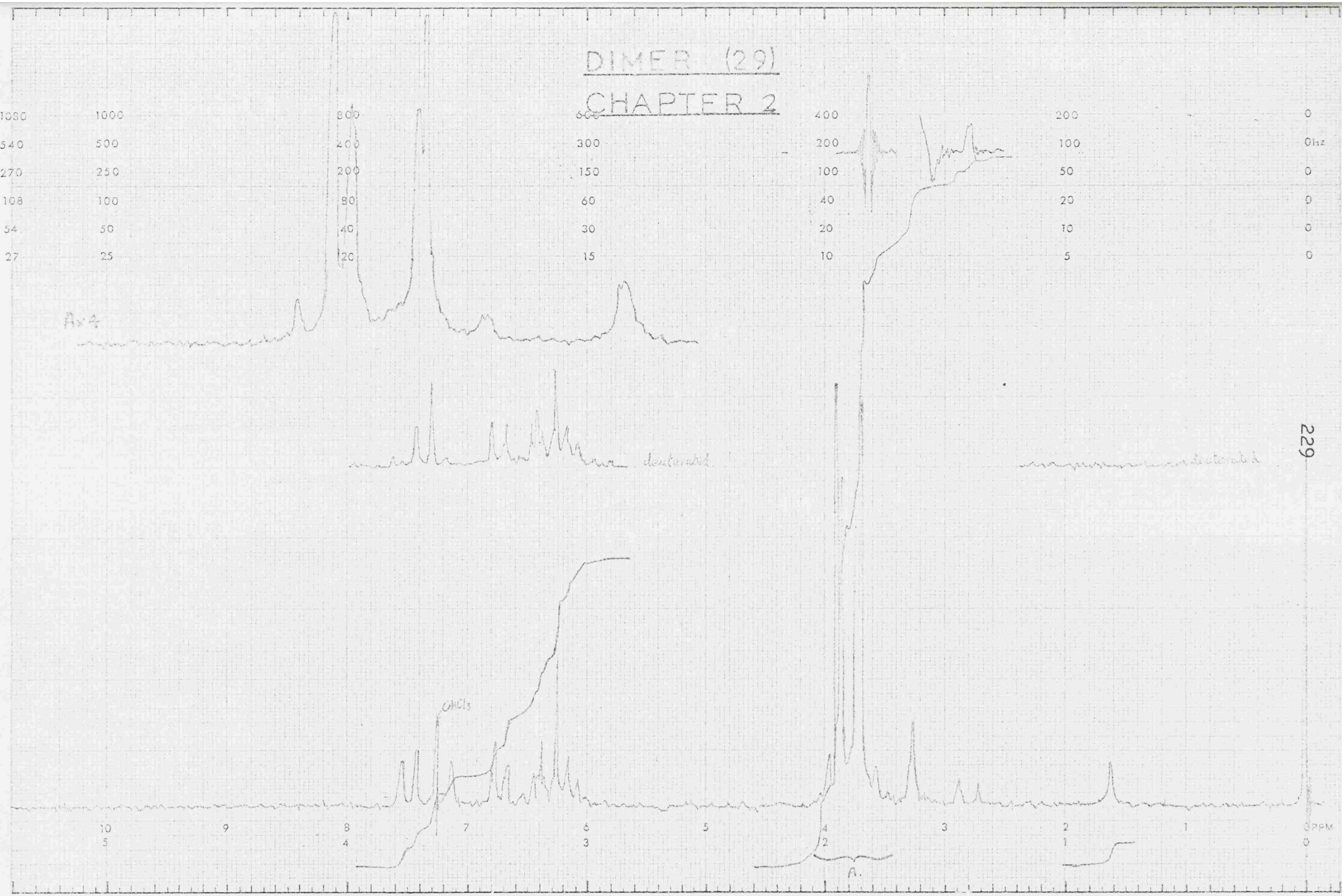
ANODIC PRODUCT (23)

CHAPTER 2



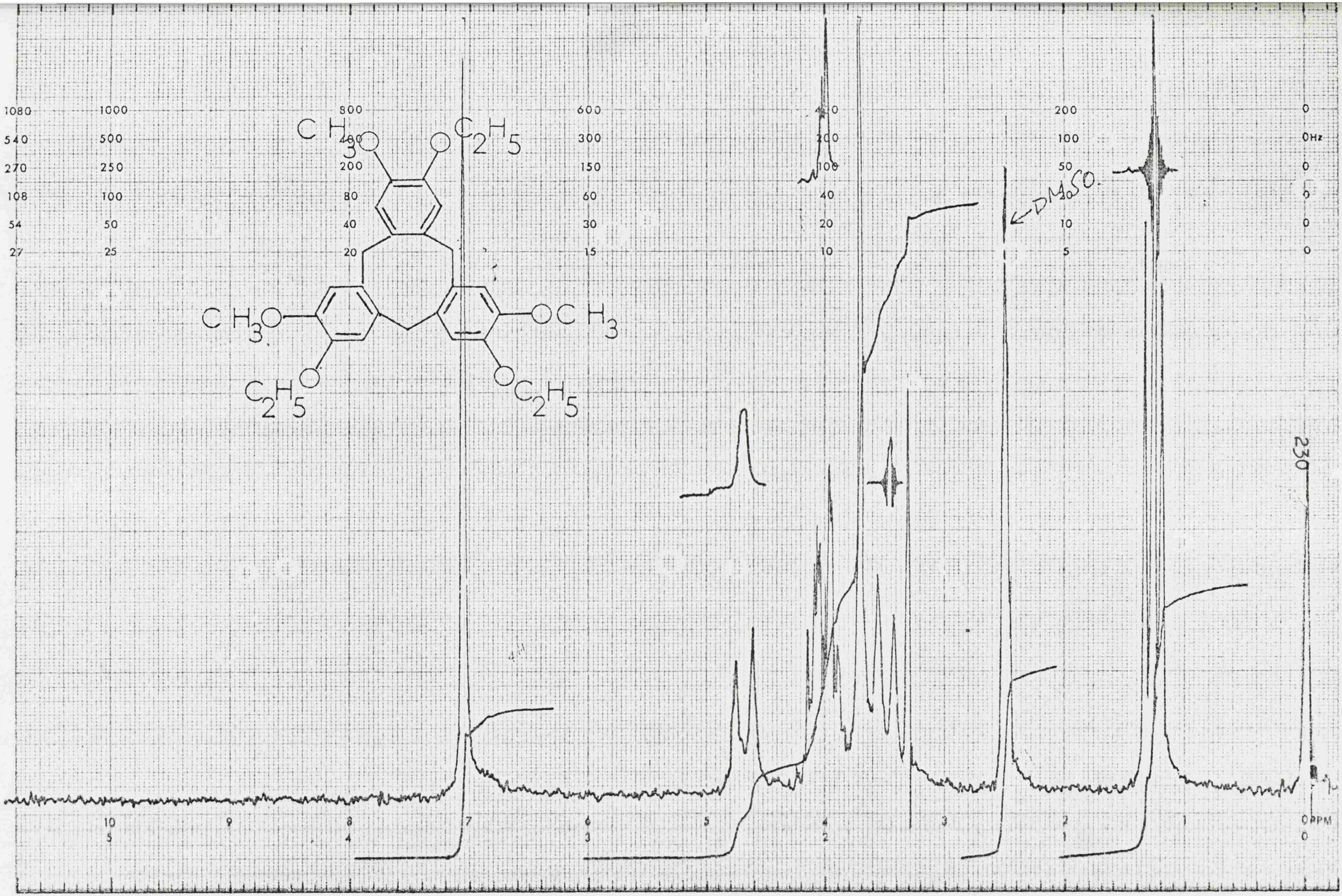
Printed in U.K.
Chart No. 4H-C


ANODIC PRODUCT (27)
CHAPTER 2
$CHCl_3$
DMSO
Printed in U.K.
Chart No. 4K-C
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.



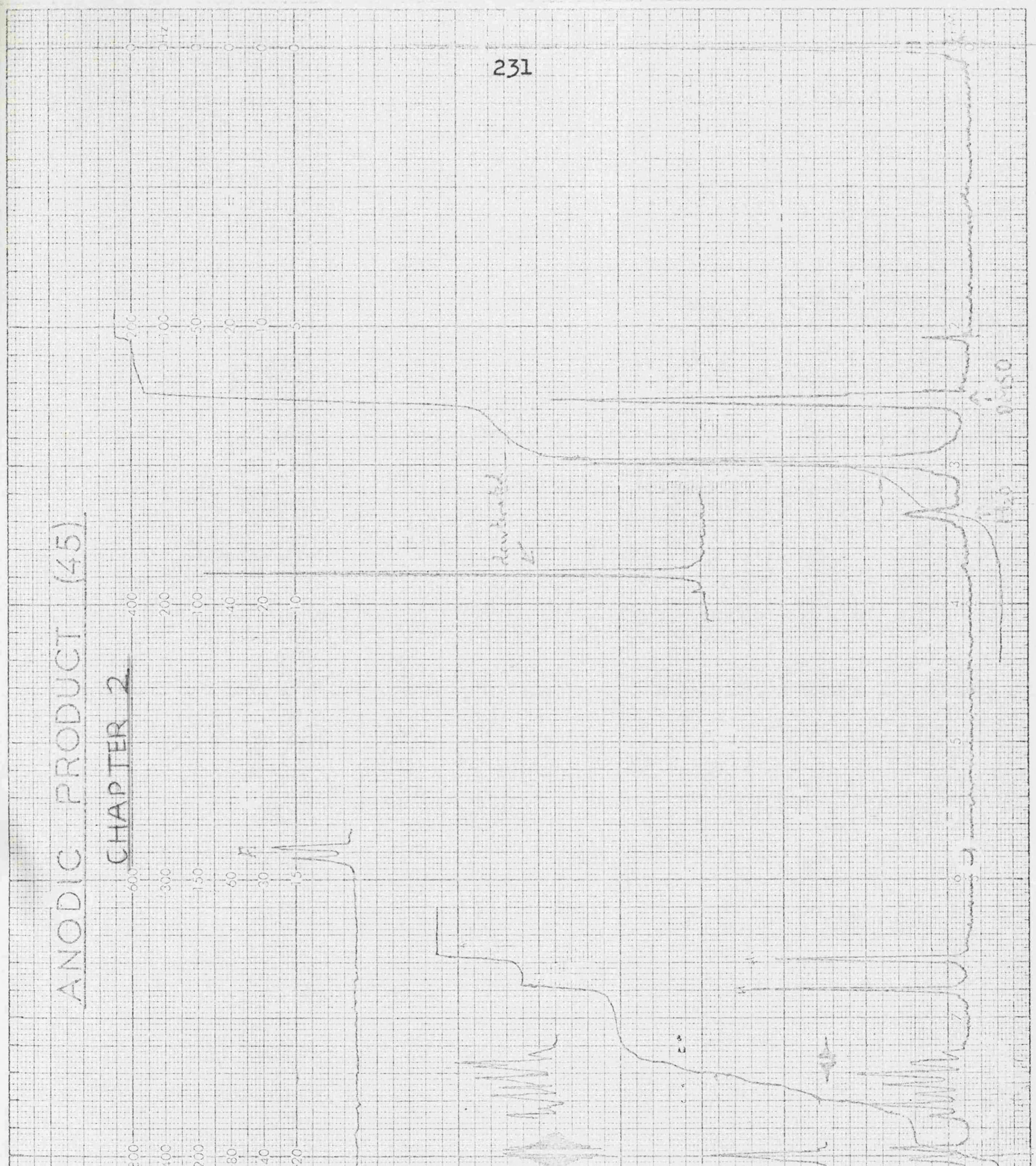
Printed in U.K.
Chart No. 4H-C

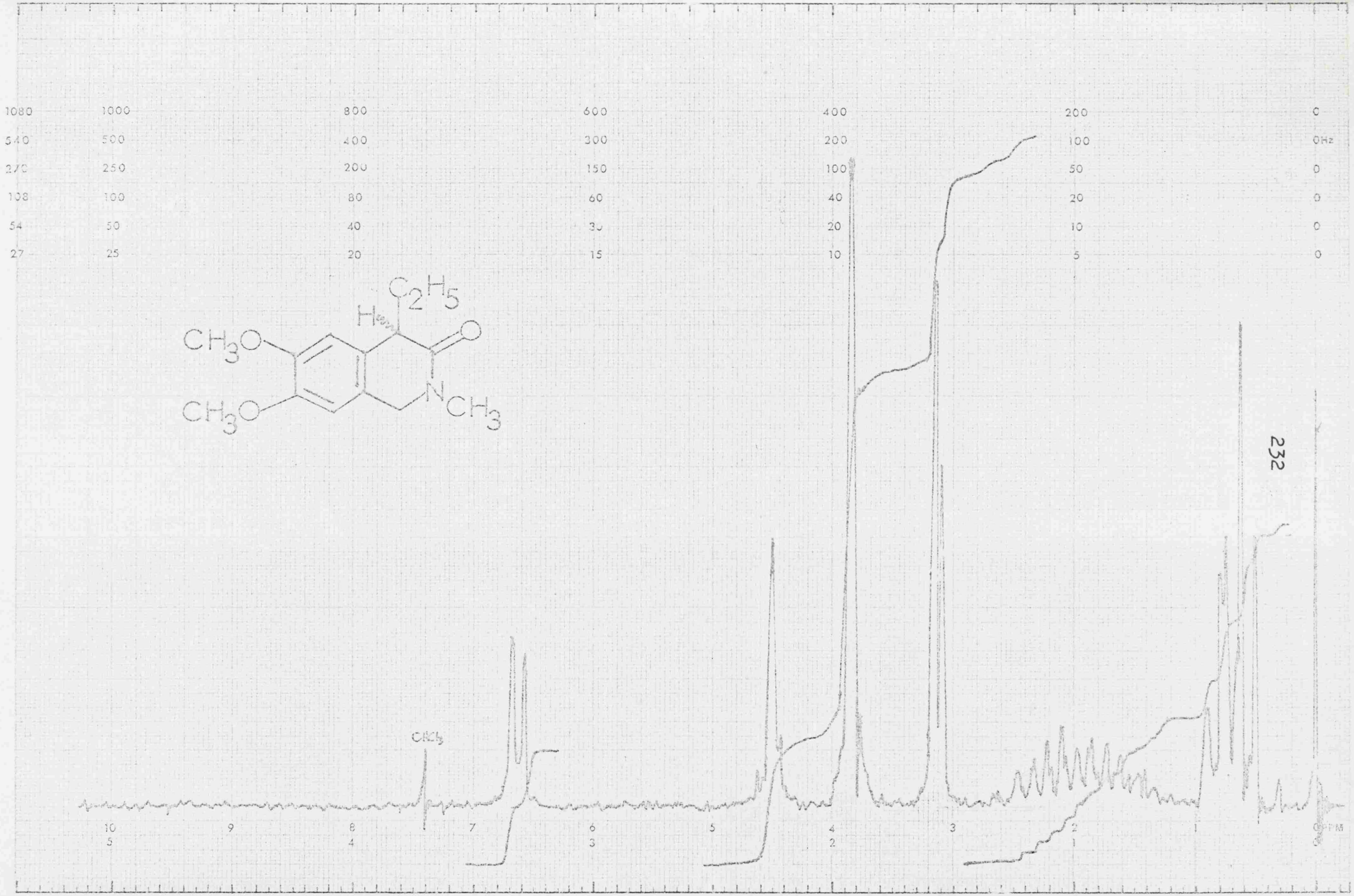
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.



Printed in U.K.
Chart No. 4H–C

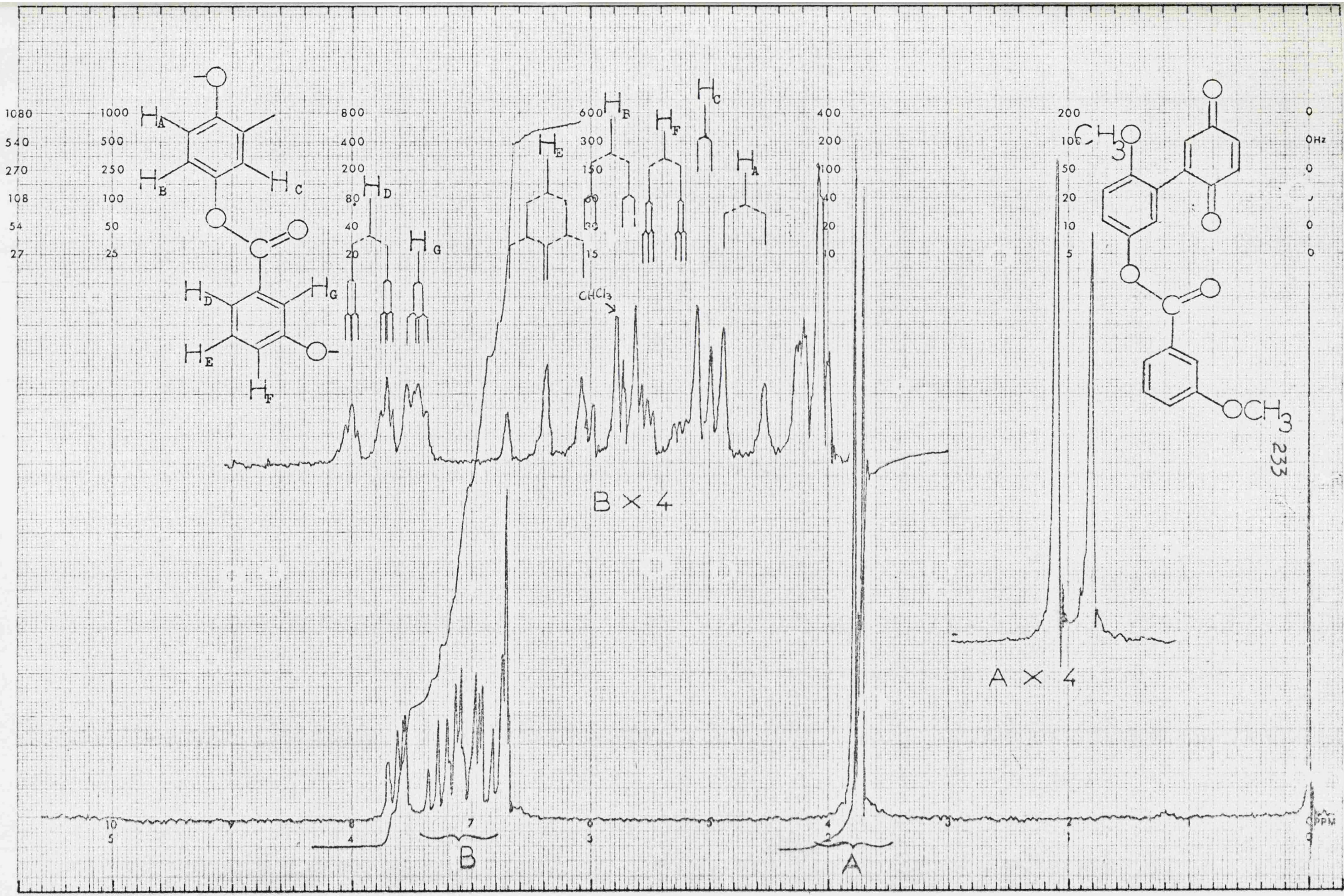
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.


ANODIC PRODUCT (45)
CHAPTER 2

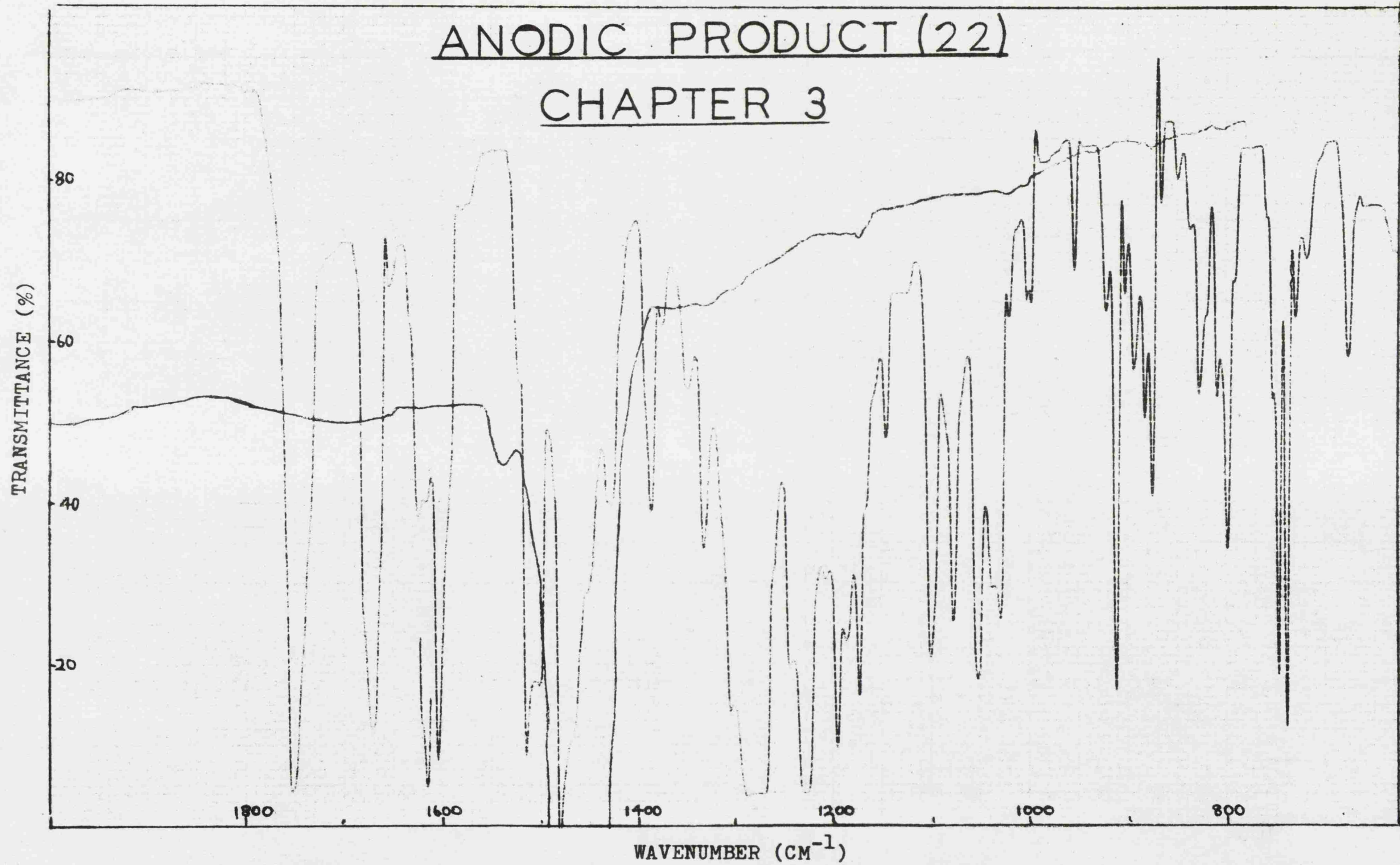


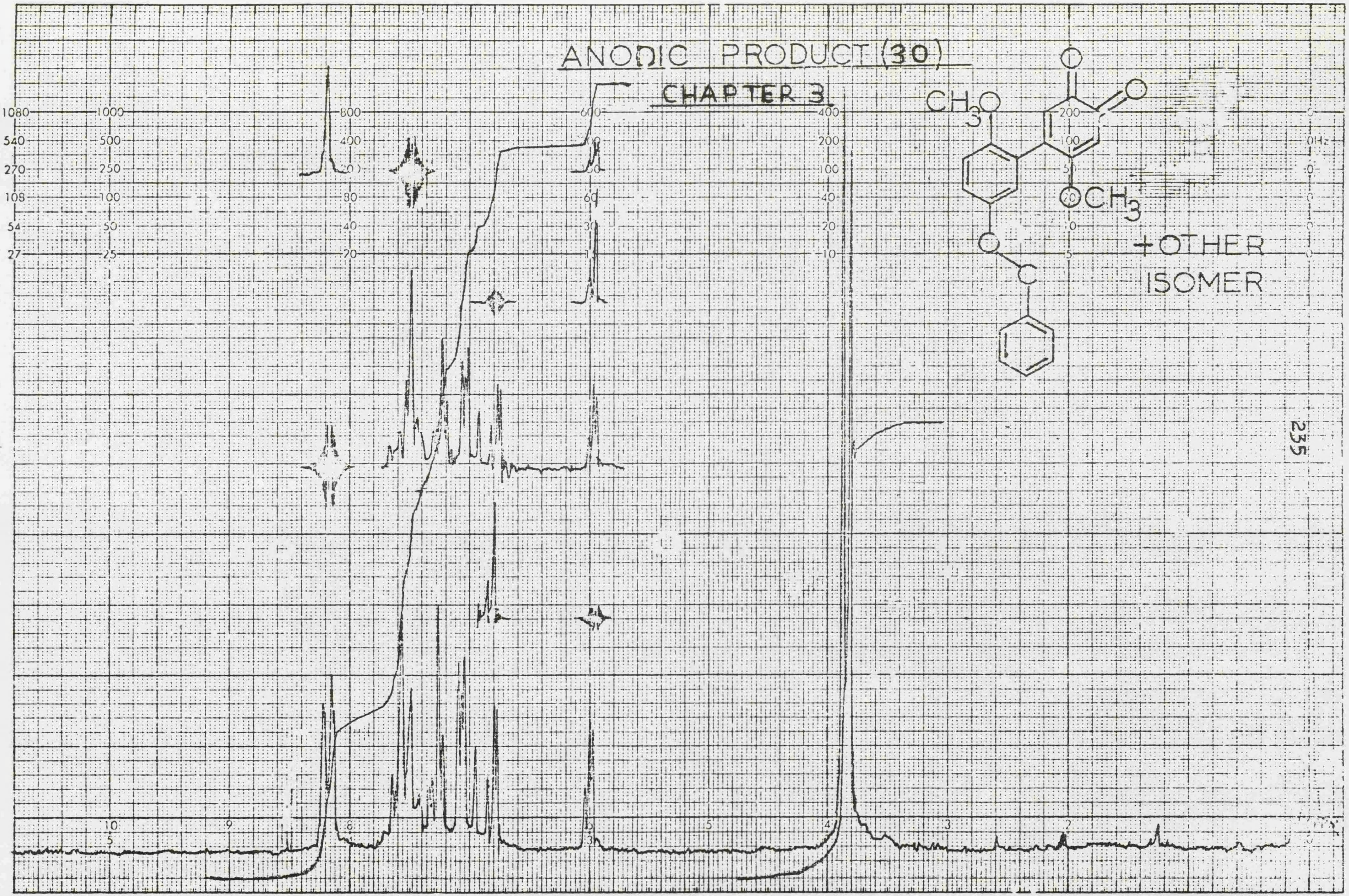
Printed in U.K.
Chart No. 4H–C

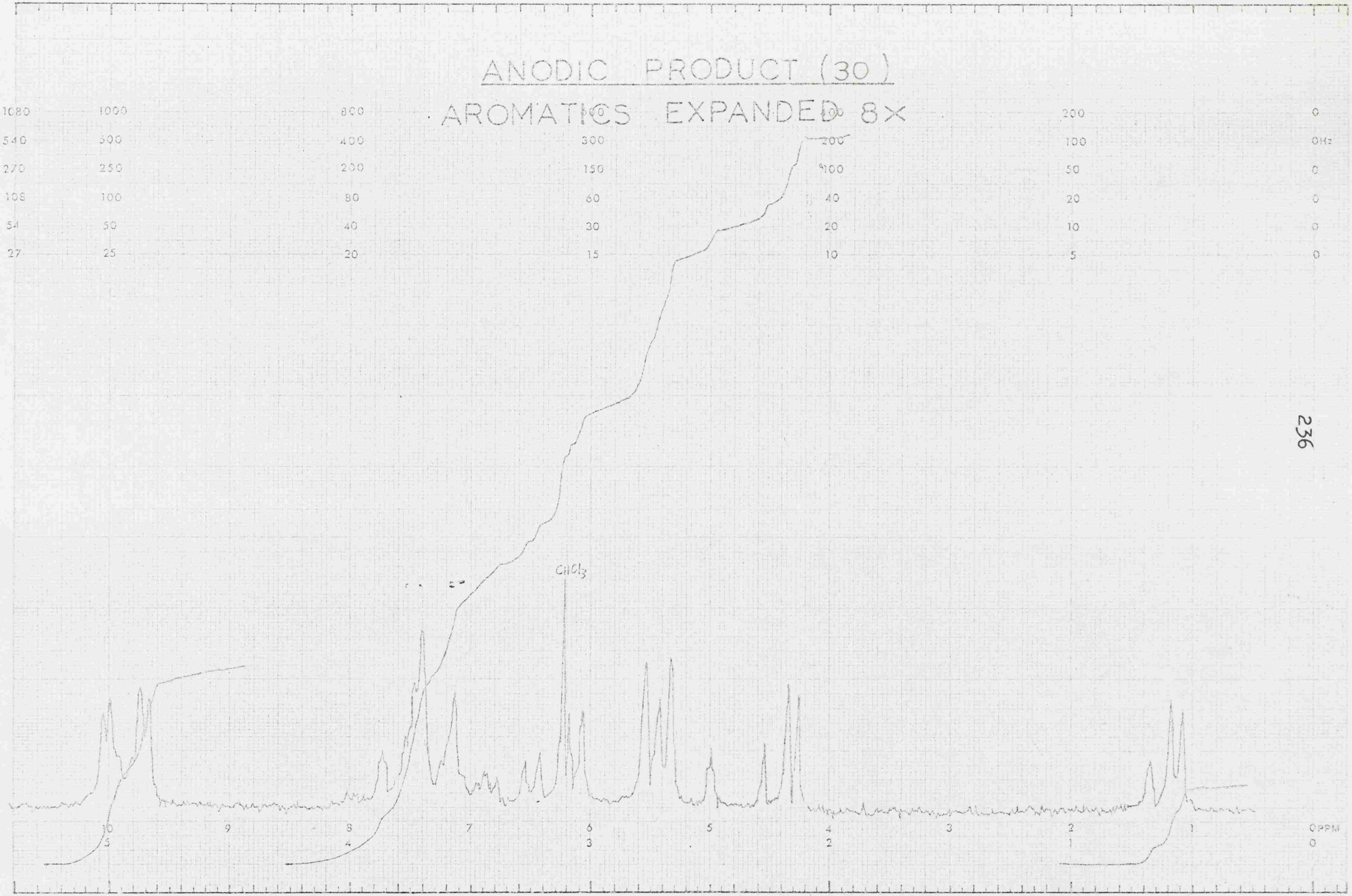
Supplied by Nuclear Magnetic Resonance Ltd., Magnetic House, Scrubbs Lane, Bledlow Ridge, High Wycombe, Bucks.

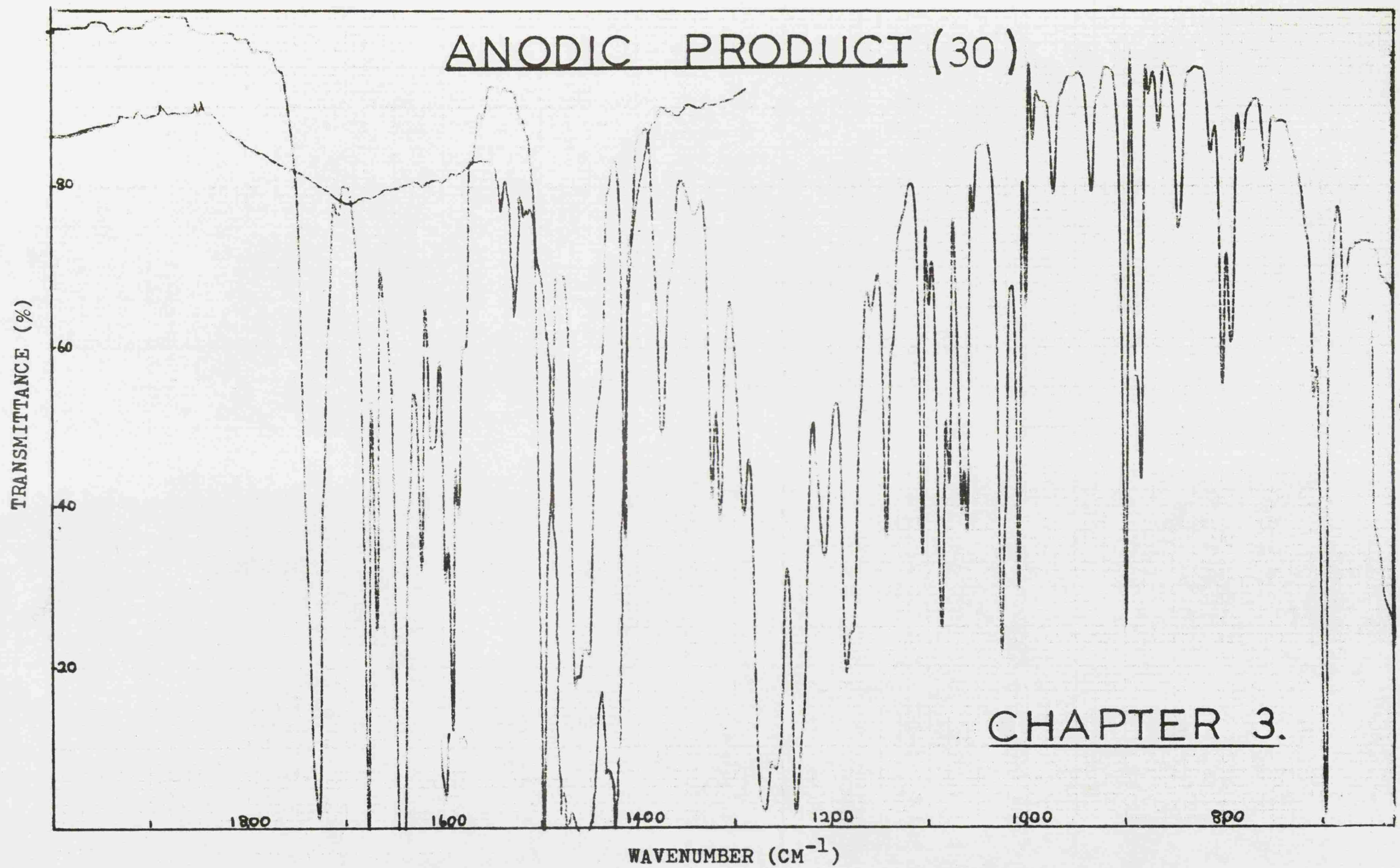


Printed in U.K.
Chart No. 4H-C


ANODIC PRODUCT (22)
CHAPTER 3
TRANSMITTANCE (%)
80
60
40
20
1800
1600
1400
1200
1000
800
WAVENUMBER (CM^{-1})

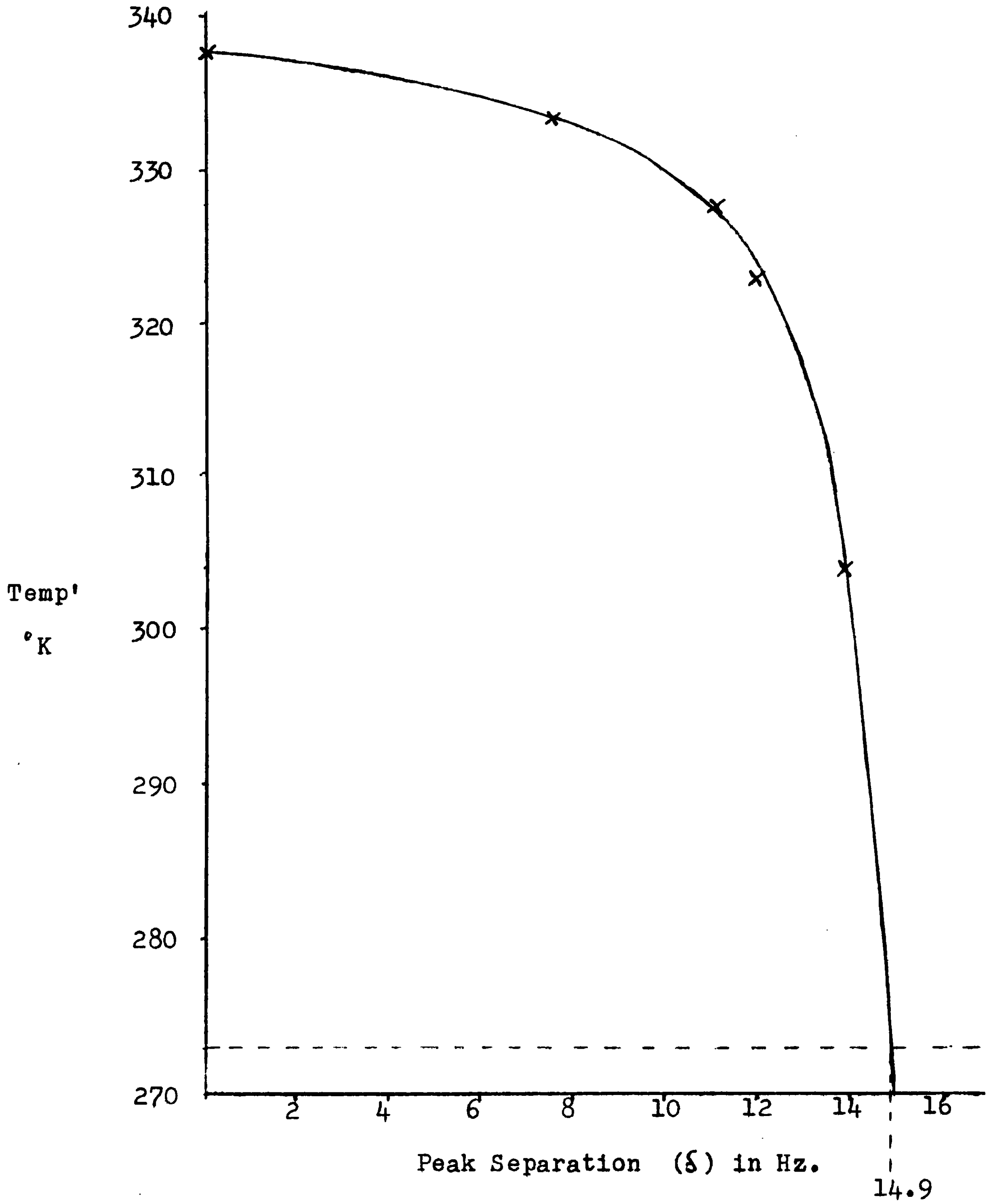

ANODIC PRODUCT (30)
CHAPTER 3
CH3O
OCH3
+ OTHER
ISOMER


ANODIC PRODUCT (30)
AROMATICS EXPANDED 8X
CHCl3
PPM



ANODIC PRODUCT (30)
TRANSMITTANCE (%)
80
60
40
20
1800
1600
1400
1200
1000
800
WAVENUMBER (CM^{-1})
CHAPTER 3.

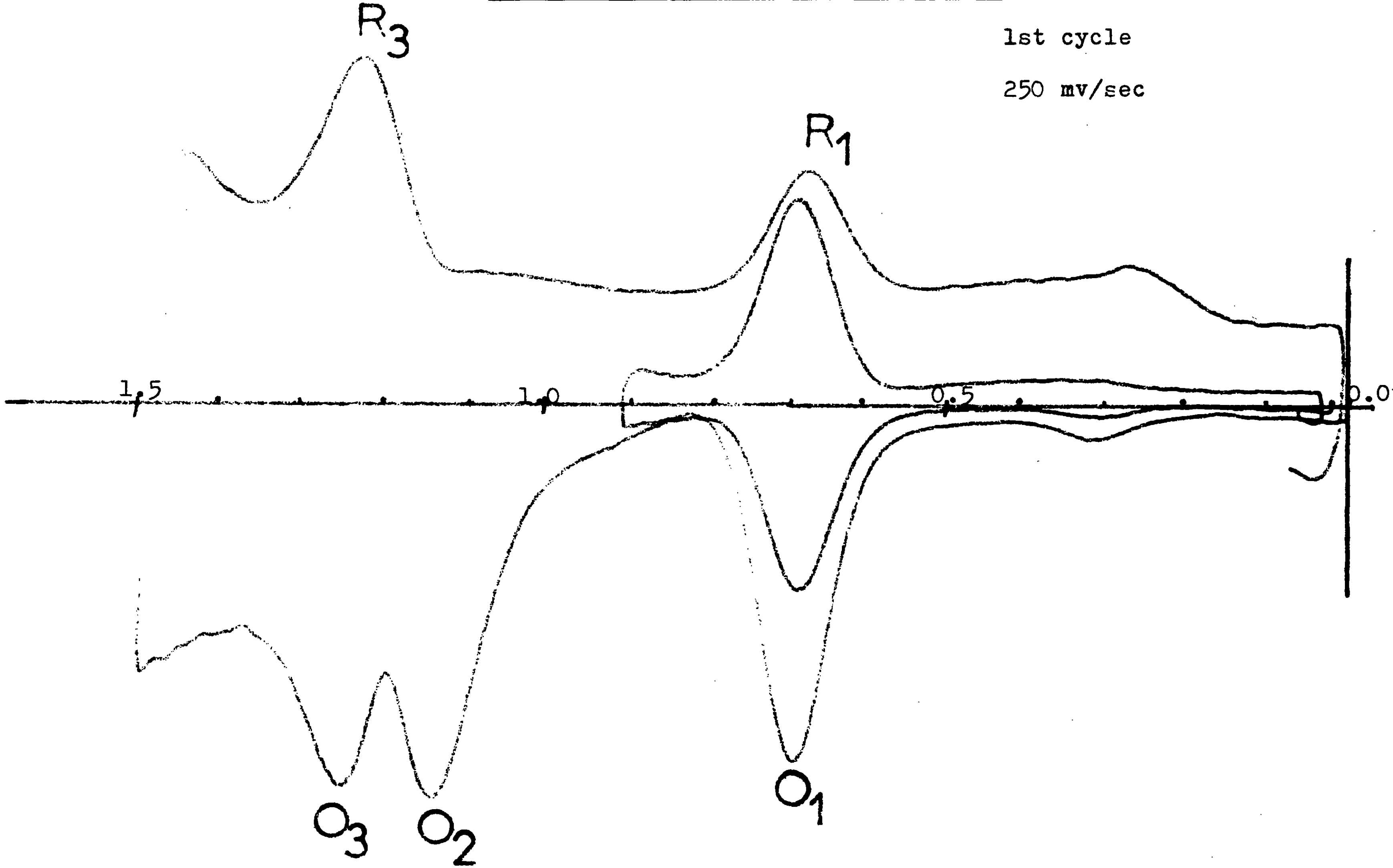
Extrapolation Graph for Amide (18) (Chapter 1)



N-veratryl-5,6-dimethoxyoxindole (7)

1st cycle

250 mv/sec

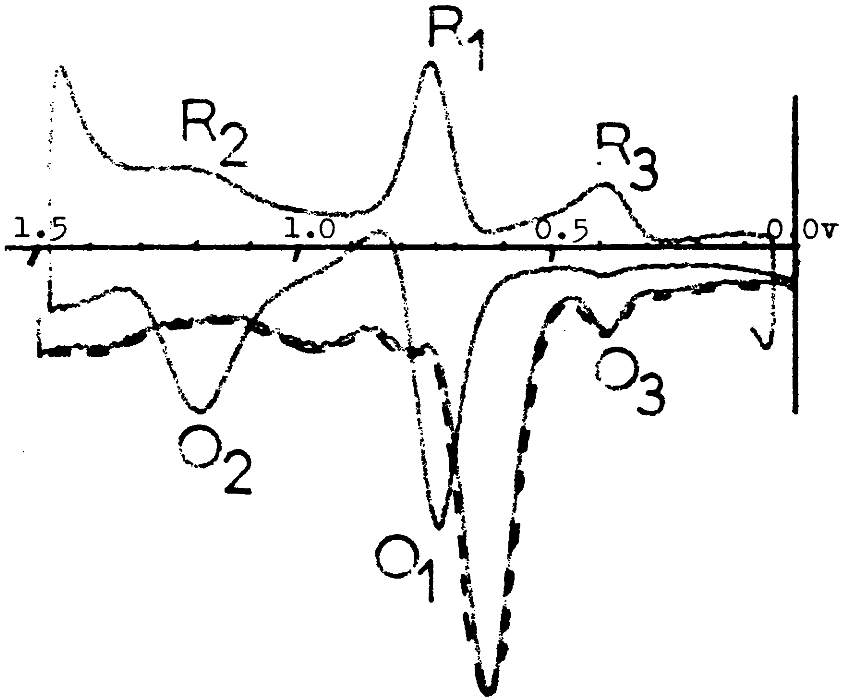


5,6-dimethoxyoxindole

On addition of pyridine

1st scan

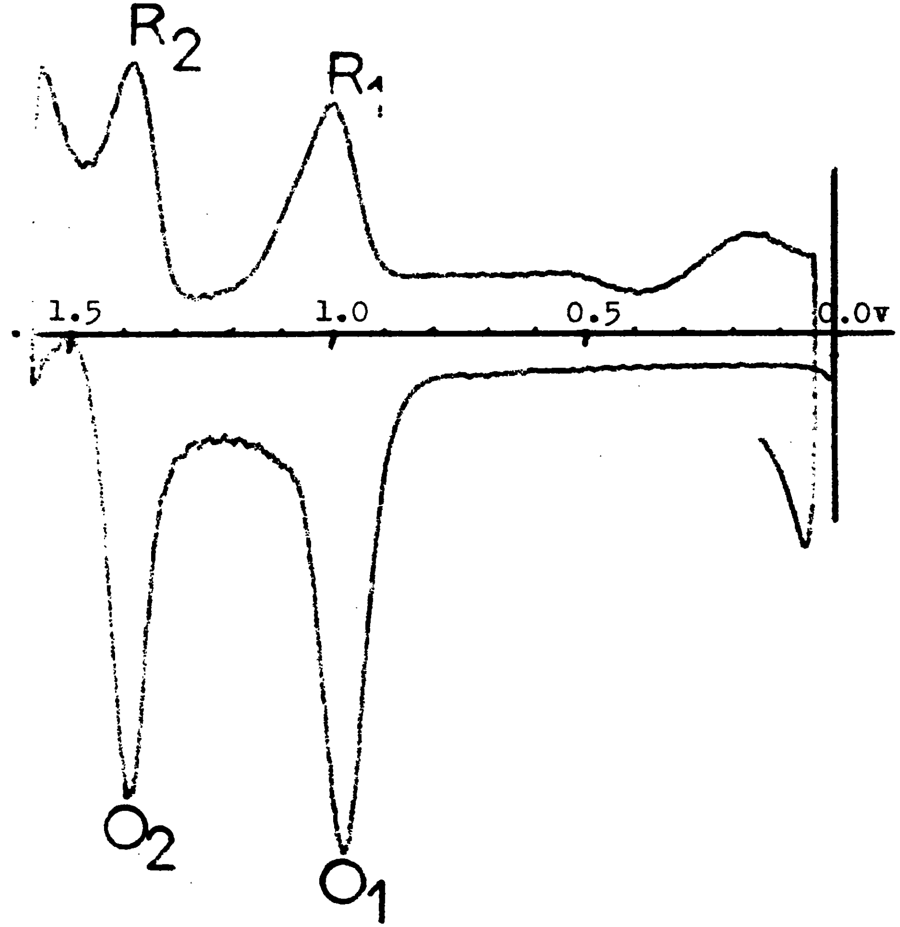
250 mv/sec



N-acetyl-5,6-dimethoxyoxindole

1st scan

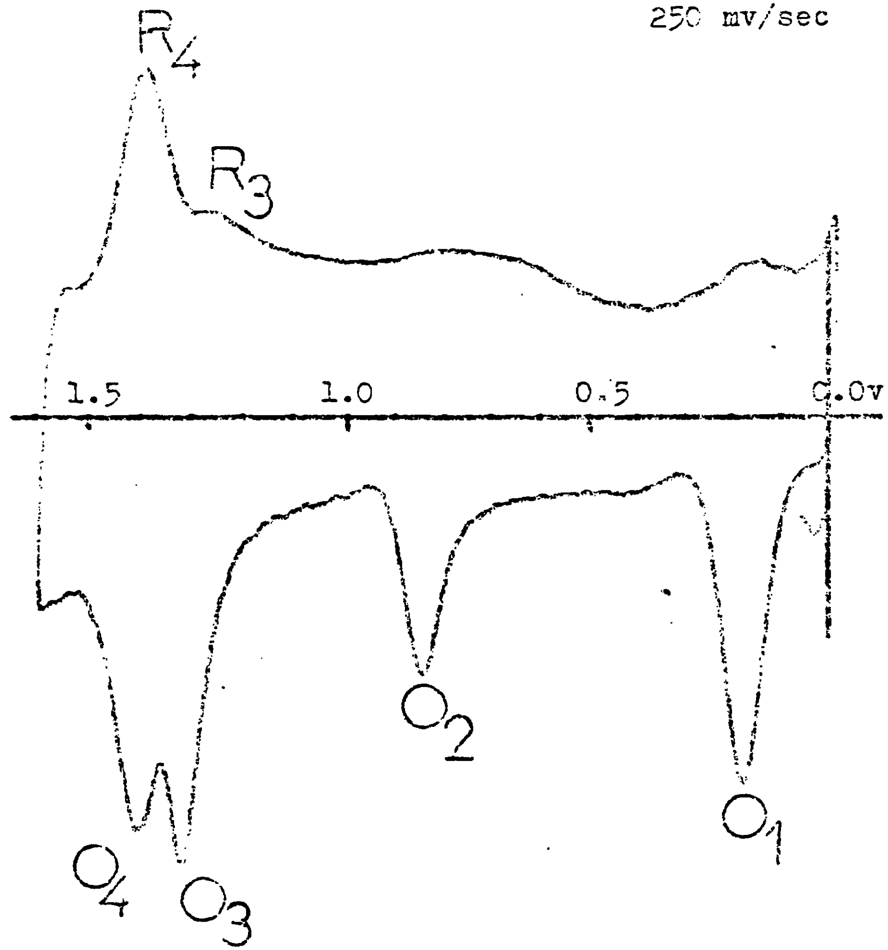
250 mv/sec



<u>1-piperonyl-5,6-dimethoxyindoline (21)</u>

1st scan

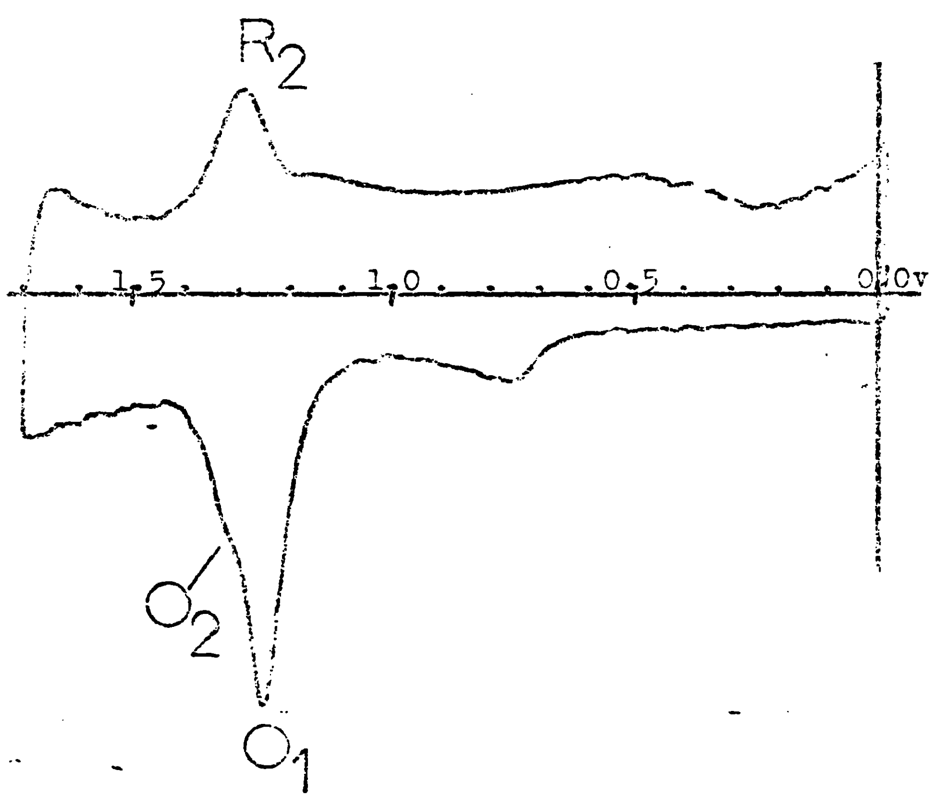
250 mv/sec



<u>Voltammogram of (21) on addition of TFA.</u>

1st scan

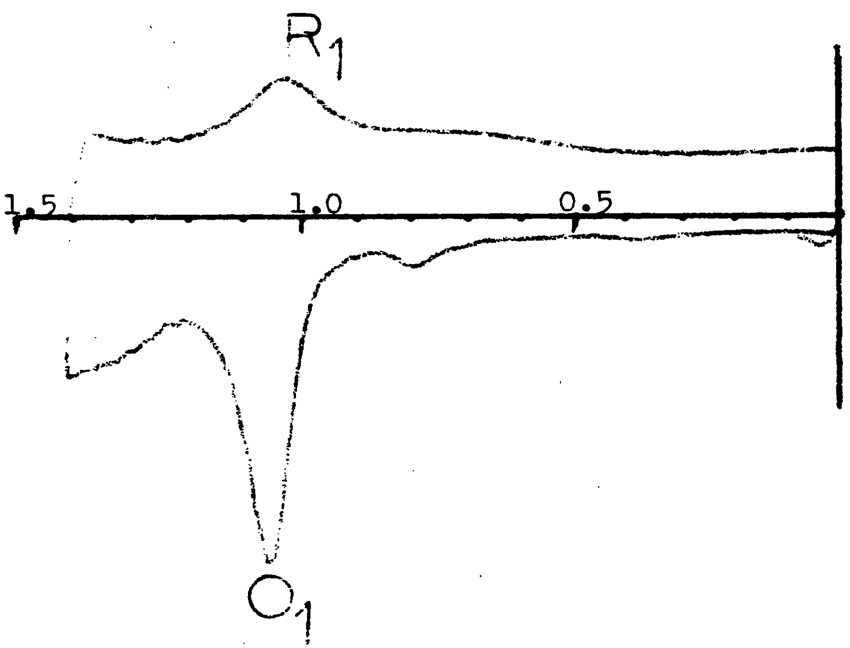
250 mv/sec



3-homoveratryl-1-acetylindole (42)

1st scan

250 mv/sec

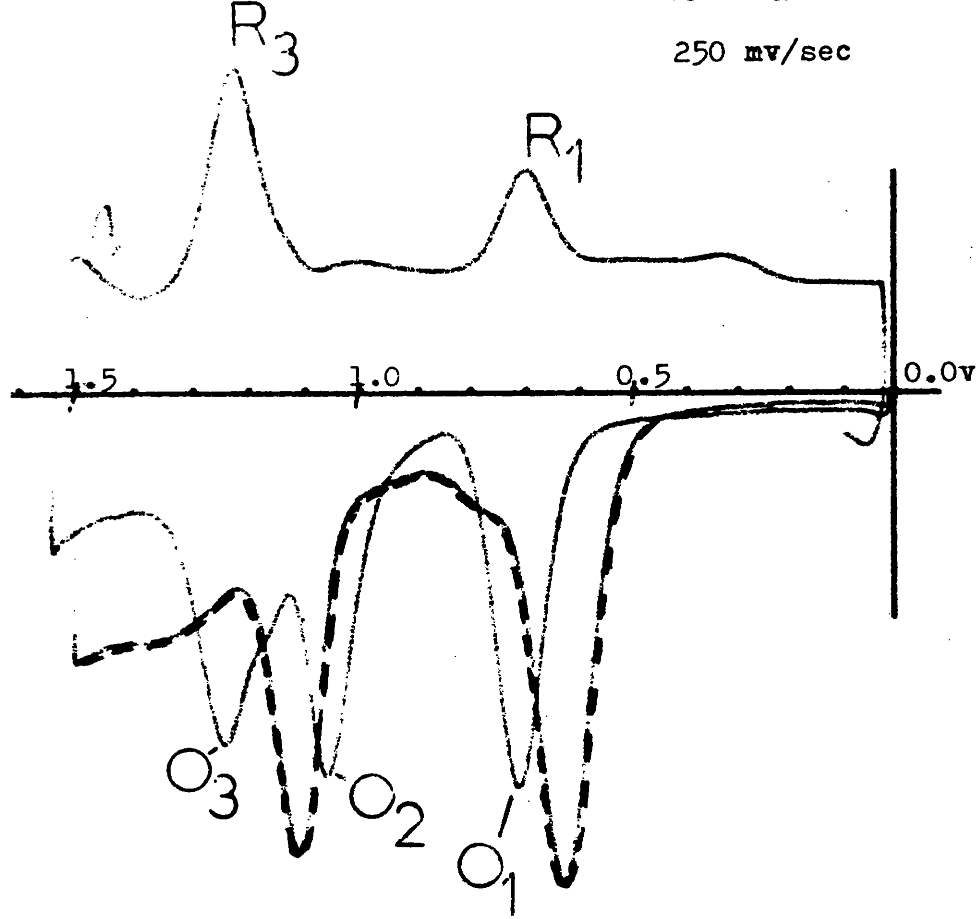


3-veratryl-5,6-dimethoxyoxindole (25)

On addition of pyridine

1st scan

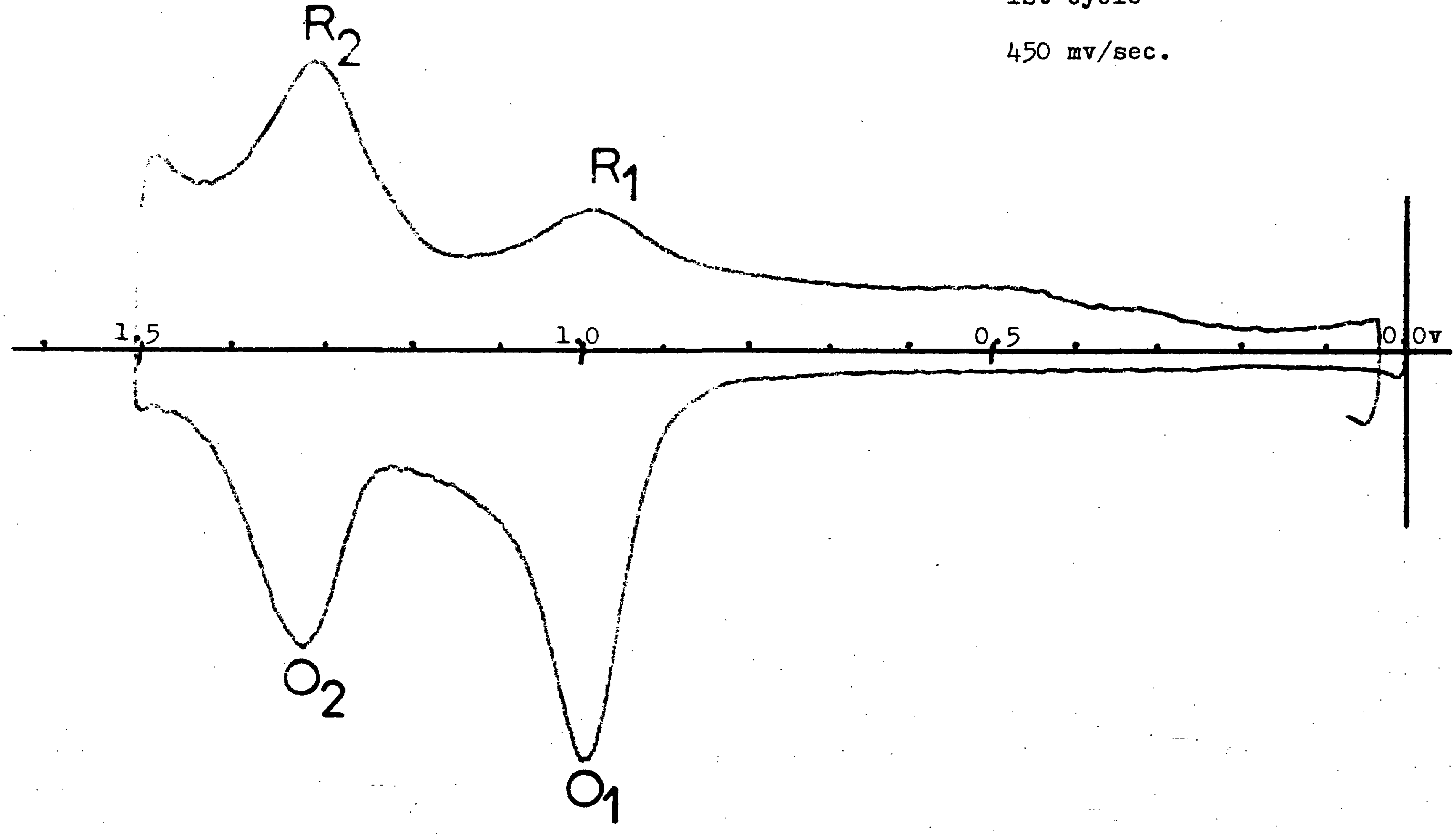
250 mv/sec



N-acetyl-3-veratryl-5,6-dimethoxyoxindole (30)

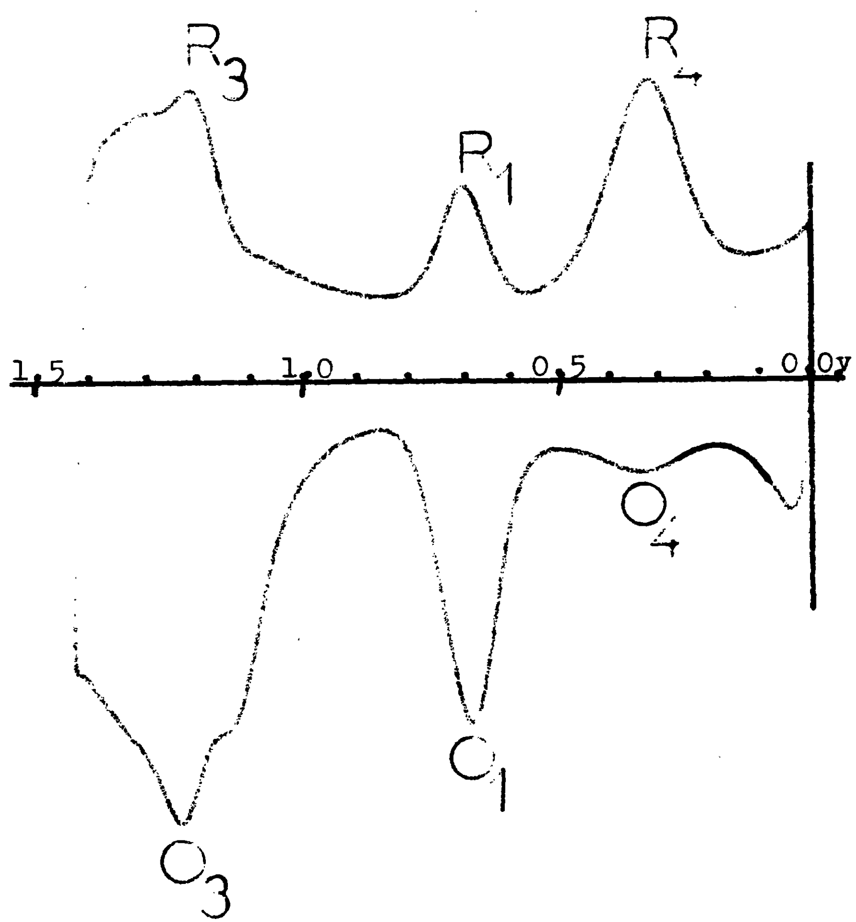
1st cycle

450 mv/sec.



Steady state voltammogram of (36)

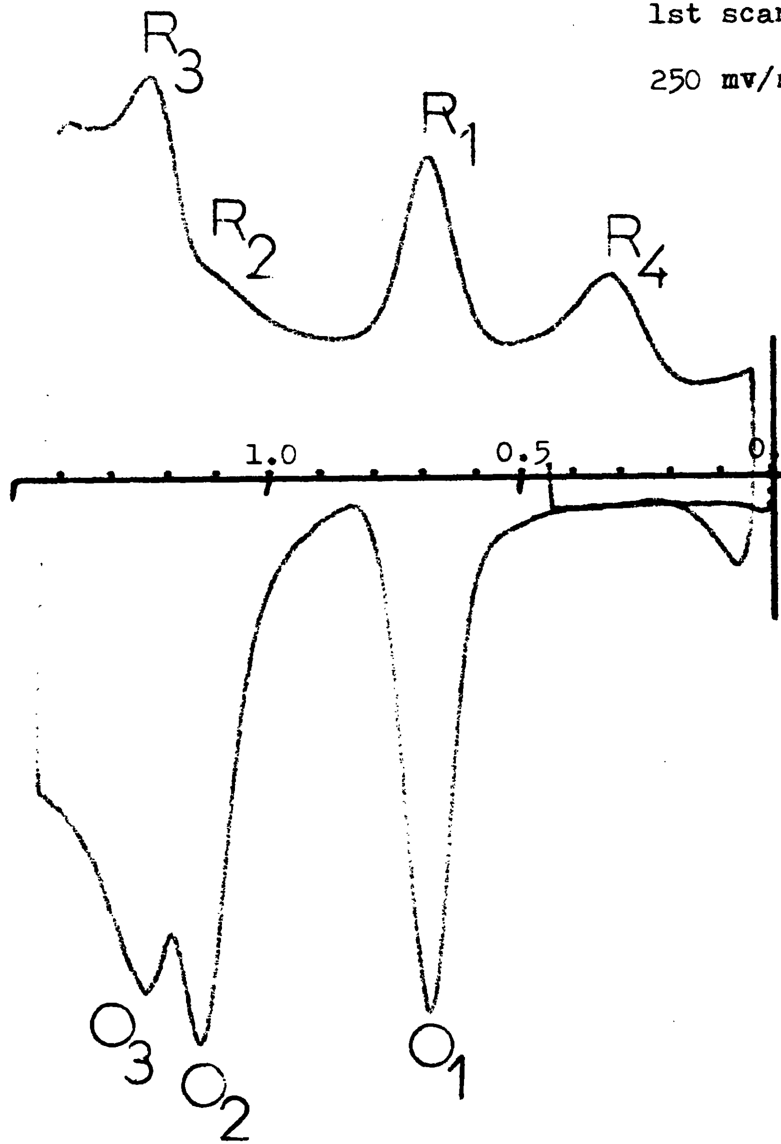
(10 cycles) 250 mv/sec



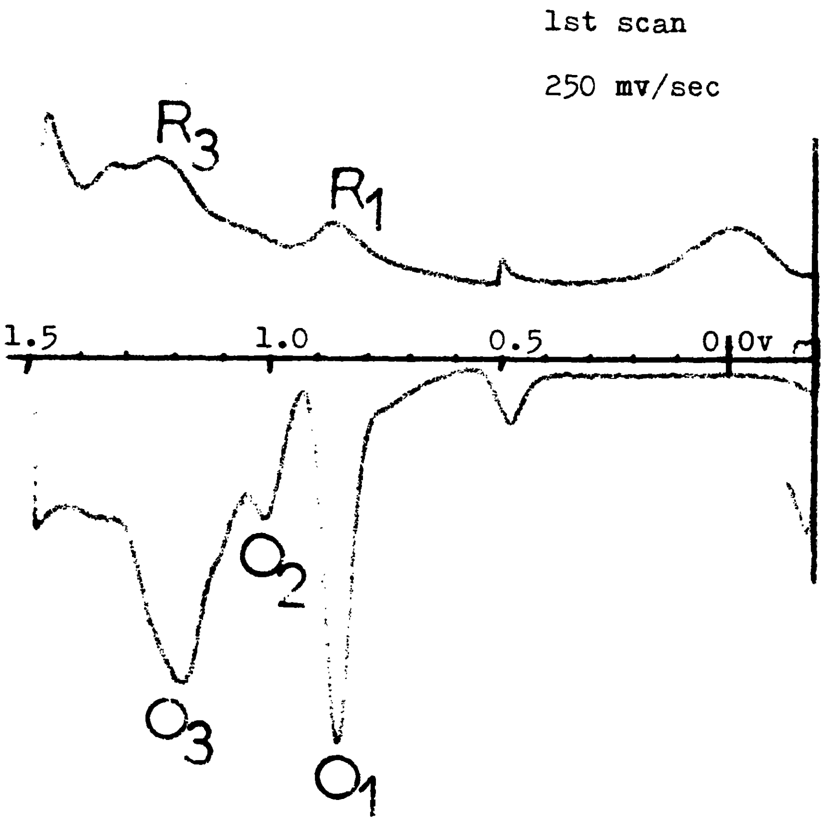
1-homoveratroyl-5,6-dimethoxyindoline (36)

1st scan

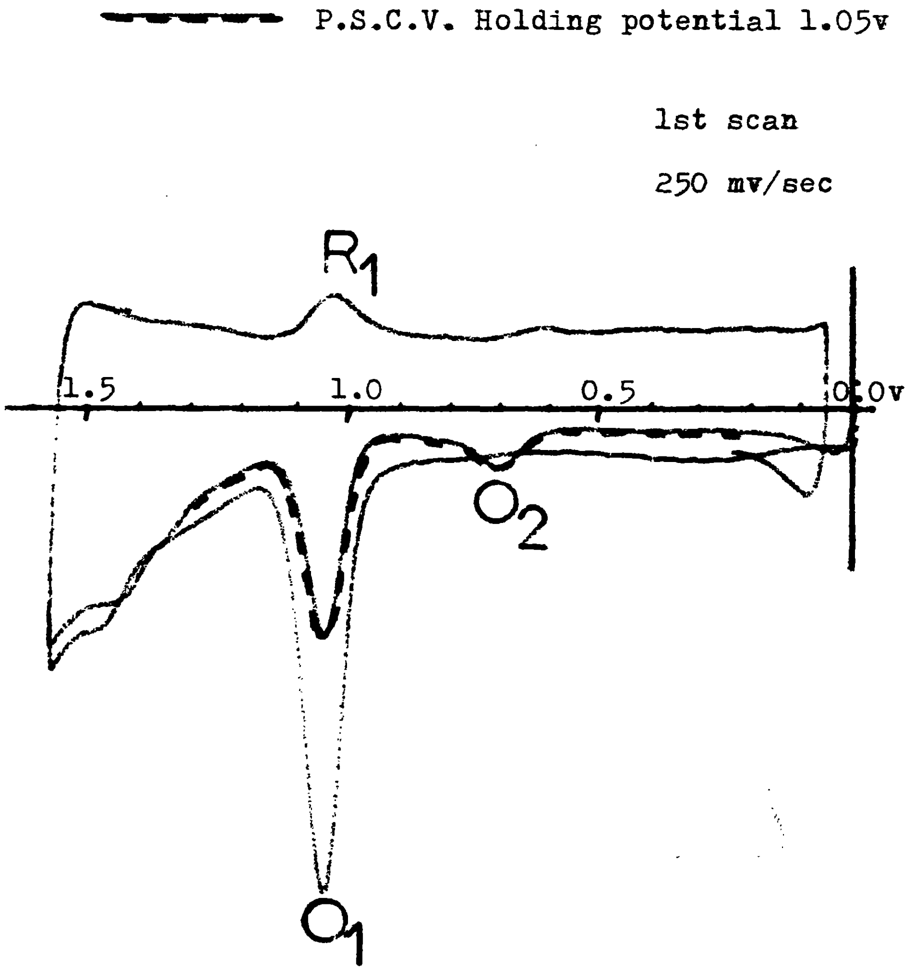
250 mv/sec



3-homoveratrylindole (39)

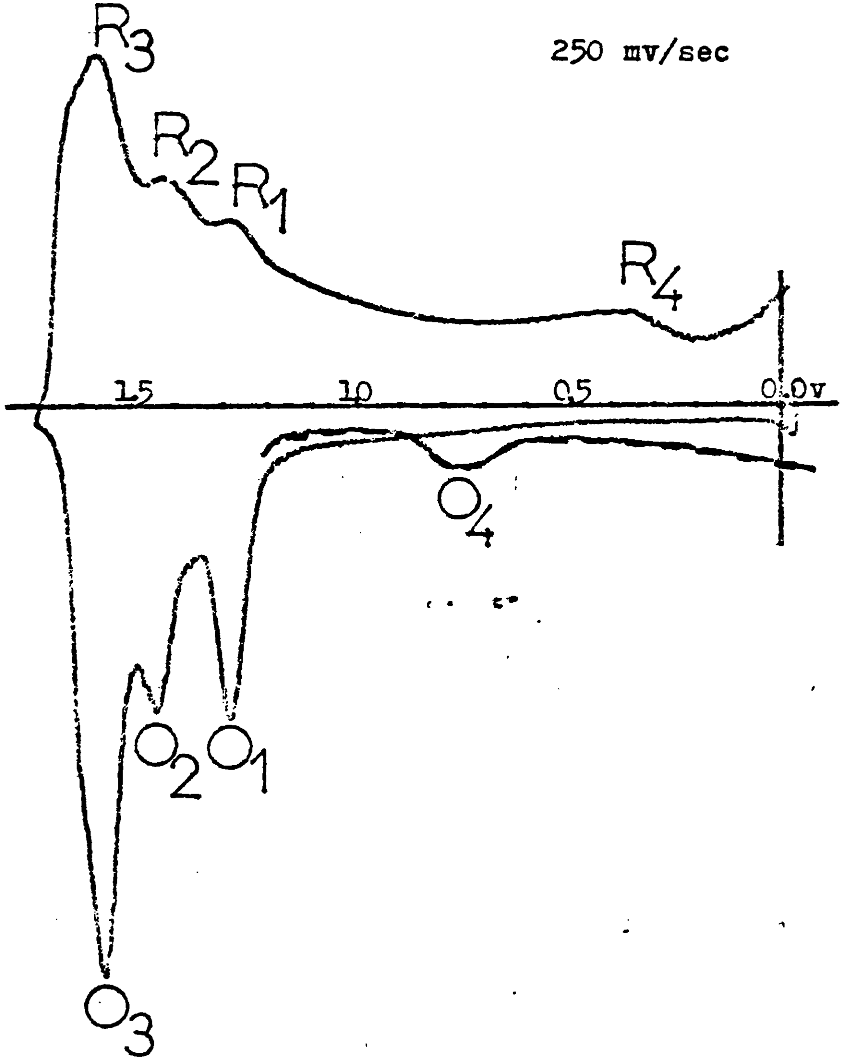


3-[β-(3,4-dimethoxyphenyl)propionoyl]indole (44)



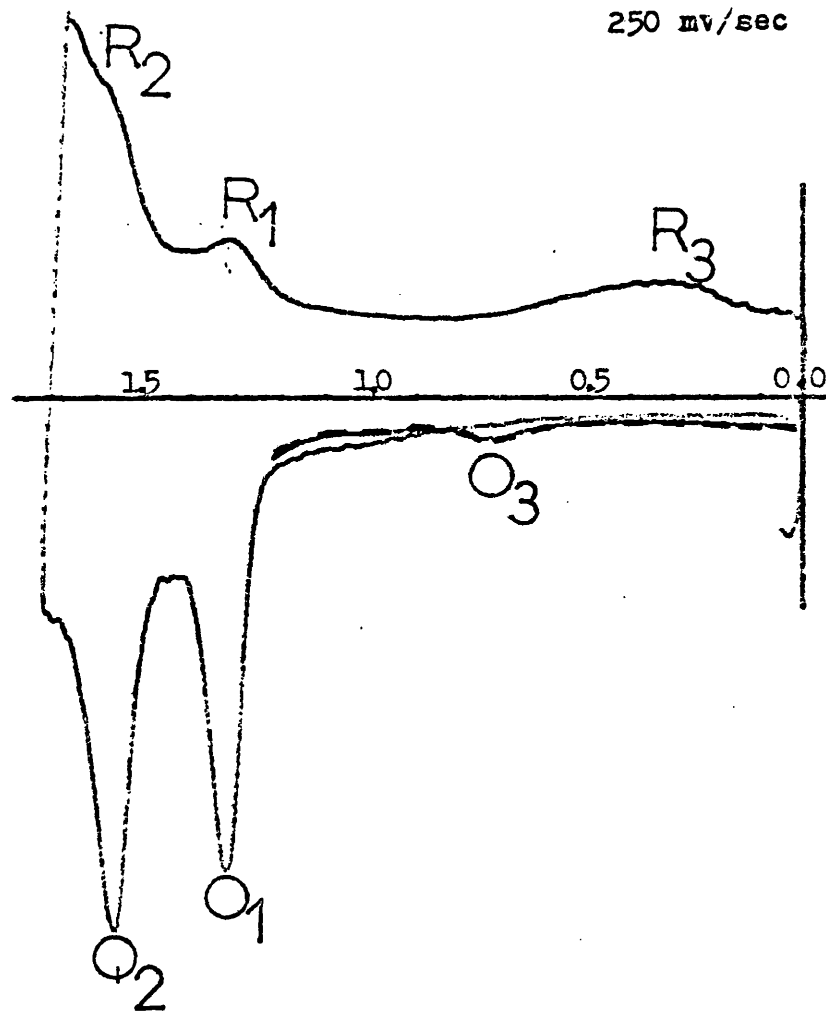
Dimer (21). (Chapter 3).

P.S.C.V. Holding potential 1.45v



4-methoxyphenyl-3-methoxybenzoate (17)

P.S.C.V. Holding potential 1.40v



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